Tinnitus : assessment of quality of life & cost-effectiveness

TINNITUS

ASSESSMENT OF QUALITY OF LIFE & COSTS

Production: Ridderprint
Cover design: Lydia Kersemakers
Lay-out: I.H.L. Maes
ISBN: 978-90-5335-789-7

The studies in this thesis were supported by grants from the Netherlands Organization for Health Research and Development (ZonMw).

Publication and distribution of this thesis was financially supported by Adelante, centre of expertise in rehabilitation and audiology and Streukens Hooroplossingen B.V. (which is a part of Schoonenberg Hoorcomfort)

TINNITUS

ASSESSMENT OF QUALITY OF LIFE & COSTS

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van Prof. Dr. L.L.G. Soete, Rector Magnificus,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen op woensdag 22 januari 2014 om 16:00 uur

door

Iris Helena Leonard Maes

Promotores
Prof. dr. M. Peters
Prof. dr. B. Kremer

Copromotores
Dr. M. Joore
Dr. L. Anteunis

Beoordelingscommissie
Prof. dr. C. Dirksen (voorzitter)
Prof. dr. S. Evers
Dr. C. Leue
Prof. dr. I. Myin-Germeys
Prof. dr. R. Stokroos

Besef

niemand ontkomt eraan
jarenlang kunnen je dagen mild zijn
en leef je in een zachte bries
van kleine zorgen
en plotseling
stormen van pijn...
het leven is dansen
tussen licht en donker
tussen eb en vloed
daartussen ligt het besef van het draaien der aarde

wie alleen maar langs kalme meren gaat
zal de vloed nooit ruiken
en het strand niet bewandelen
achter het terugwijkend getijde

maar zeg dat niet tegen wie vecht in de branding
- gooi dan een lijn uit.

TINI VISSER

Voor Pap en Mam

Voor Mila en Elin

CONTENT

General introduction		9
Chapter 1	Assessment of health state in patients with tinnitus: a comparison of the EQ-5D and HUI Mark III	15
Chapter 2	Tinnitus: A cost study	29
Chapter 3	Specialized treatment based on cognitive behavioral therapy versus usual care for tinnitus: a randomized controlled trial.	41
Chapter 4	Cost-effectiveness of specialized treatment based on cognitive behavioral therapy versus usual care for tinnitus	63
Chapter 5	Measuring health-related quality of life by experiences: the Experience Sampling Method	81
Chapter 6	The effects of tinnitus on daily life: an experience sampling study	103
Summary and discussion		117
References		127

GENERAL INTRODUCTION

Tinnitus

Tinnitus is the perception of a pernicious, and for some disabling sound for which there is no acoustic source. The most recent study on the prevalence of tinnitus reported that 16-21% of the adult population are bothered by tinnitus at some point in their life and 2-4% was almost always bothered by it (Krog et al., 2010). Earlier studies have shown that 10–15% of the general population experience tinnitus severely enough to seek medical attention (Heller, 2003) and 3-5% of the population is severely impaired by the tinnitus (Davis & El Refaie, 2000; Vesterager, 1997). Among hearing impaired individuals prevalence has been estimated at 75% to 80% (Adams et al., 1999). Tinnitus may be a symptom of one or more underlying pathologies (Newman et al., 2011). In most patients with (bilateral) tinnitus, there is no underlying medical condition. There are several theories on the etiology of tinnitus that is not explained by an underlying pathology but scientific evidence remains absent. As a result patients seek help in various areas of health care, but most of the therapies do not lead to recovery. Patients with severe tinnitus often experience affective problems, sleep difficulties and major impact upon concentration (Bartels et al., 2008; Davis & El Refaie, 2000; Henry et al., 2005). When comparing tinnitus patients to healthy controls or non-help seeking tinnitus sufferers, patients with tinnitus experience higher levels of depression and anxiety (Attias et al., 1995; Scott & Lindberg, 2000). Interference with daily activities such as social activities, self-care activities, and occupational activities have been demonstrated as well (Cima, Vlaeyen et al., 2011; Folmer et al., 1999; Hiller & Haerkotter, 2005). However, information on whether fluctuations in tinnitus severity are related to emotional, social and behavioral interference in daily life, is virtually lacking.

Treatment of tinnitus

In the Netherlands, most patients with tinnitus who do consult their GP do so within six months after onset of the complaints, but one quarter of the patients wait several years until they seek help (NIPO, 2002). A frequently consulted specialist is the ENT (ear, nose and throat) physician. Treatment possibilities include removal of cerumen, middle ear surgery, medication, and audiological rehabilitation. Audiological rehabilitation involves counseling, hearing aid fitting to compensate hearing loss or provide sound generators or tinnitus maskers. There is mixed evidence to support the clinical effectiveness of these treatments (Hoare et al., 2010; Hobson et al., 2010). Over the years evidence regarding the efficacy of other clinical interventions remains sparse, but there are indications of benefit from Tinnitus Retraining Therapy (Forti et al., 2009; Henry et al., 2007; Henry et al., 2002; Phillips & McFerran, 2010), Cognitive Behavioral Therapy (El Refaie et al., 2004; Gudex et al., 2009; Hesser et al., 2011; Martinez-Devesa et al., 2010) and a combination of therapies (Hoare et al., 2010). Tinnitus Retraining Therapy (TRT) is based on the neurophysiologic model of tinnitus developed by Jastreboff (Jastreboff et al., 1996). TRT involves 1) extensive directive counseling about tinnitus to reduce aversive reactions to the symptom and 2) sound therapy to facilitate habituation to the tinnitus signal (Jastreboff et al., 1996). Evidence to support TRT is mostly derived from retrospective and uncontrolled trials (Hiller & Haerkotter, 2005; Hoare et al., 2010; Phillips & McFerran, 2010). Cognitive behavioral therapy is used to alter psychological processes that are considered to maintain or contribute to tinnitus-related complaints. This treatment usually involves psycho-education, relaxation, exposure techniques and behavioral reactivation. Treatments that combine counseling and audiologic rehabilitation are also effective (El Refaie et al., 2004; Gudex et al., 2009). Although different therapies can be effective in reducing distress and improving quality of life, large scale and well controlled trials are needed (Cima et al., 2012). A stepped-care approach in which the intensity of cognitive behavioral therapy varies, depending on the severity of tinnitus complaints has never been tested. In this thesis the cost-effectiveness of a specialized,

stepped-care cognitive behavioral approach with elements from tinnitus retraining therapy compared with care as usual in the Netherlands, was assessed in a randomized controlled trial.

Quality of life

As mentioned in the previous paragraph almost all therapies for tinnitus aim at improving quality of life. Quality of life as an outcome measure in cost-effectiveness analysis is usually expressed in a utility score, ranging from 0 to 1, where 0 represents death and 1 represents perfect health. A standard gamble task (SG) is considered as the gold standard for measuring utilities, although the time trade-off (TTO) is mostly preferred since it is easier to administer (Drummond et al., 2005). In a SG respondents are asked to choose between two alternatives: remaining in a state of ill health for sure, or an intervention with two possible outcomes, either restoring perfect health (p) or dying immediately (1-p). The risk a respondent is willing to take (p) represents the utility score. In a TTO respondents are asked to choose between remaining in a state of ill health for a period of time A, or being restored to perfect health for a shorter period of time B. The utility of the ill health state equals B divided by A.
In most economic evaluations of health care, utilities are measured indirectly by using multi-attribute utility instruments, such as the EuroQol 5D or the Health Utilities Index Mark III.
These instruments consist of a multi-attribute retrospective description of health for self-report, and a formula to convert this description into a population health utility value. This formula is derived using valuation techniques, such as the SG and the TTO, in the general population. The problem with using different multi-attribute utility measures is that each instrument differs in conceptualization and operationalization of health, and the valuation method upon which the utility scores are based. Therefore the use of utility measures in specific populations such as tinnitus should be tested to determine which one is most responsive to change. Furthermore it is well-known that problems arise when the questions to obtain health descriptions and health utility values are ambiguous and difficult to understand, or when it exceeds participants' knowledge and the limits of memory. A problem that has been described is for instance that members of the general public are not able to imagine the experience of different health states. Many problems on self-report measures can be weakened by asking questions in close temporal proximity to the event of interest (Schwarz, 2011). It is argued that the direct measurement of people's experienced utility may be a substitute or a complement to QALYs that are inferred from choices people make. It was suggested to measure experienced utility with the Experienced Sampling Method (ESM), but it has not been tested. The ESM was designed to measure hedonic and affective experience derived from immediate reports of current subjective experience, and is thought to be a more accurate reflection of experience. In this study the potential value of using the ESM to obtain momentary accounts of a person's own HRQOL was explored and compared to a retrospective valuation of HRQOL.

Cost of tinnitus

In a cost of illness study the costs of a condition to society are calculated. The aim of such a study is to highlight the economic importance of a particular disease. There are two approaches to a cost of illness study: top-down or bottom-up. In a top-down approach the total costs per healthcare sector in a country are used as a starting point, and fractions of these costs are attributed to a specific disease. In a bottom-up approach data on healthcare consumption or cost data from a sample of patients are gathered and extrapolated to the total population. Although tinnitus treatment has been described as fragmentized and costly to both the patients and the society at large (Henry et al., 2005; Lockwood et al., 2002; Reich, 2002), a cost of illness study was not previously performed. Also, information on demographic and disease characteristics that might influence healthcare utilization is lacking. In this thesis, baseline

data from a randomized controlled trial investigating the cost-effectiveness of a specialized, stepped-care cognitive behavioral approach for tinnitus compared with usual care was used to examine the costs of tinnitus in The Netherlands from a healthcare and a societal perspective.

Economic evaluation

Cost-effectiveness of an intervention is gaining more importance in the current budget restraint healthcare systems. In a cost-effectiveness analysis costs and consequences of alternative treatment strategies are identified, measured, valued and compared. The incremental effectiveness of an intervention is quantified and compared with its incremental costs. Effectiveness can be measured using various outcomes like life years saved. In most guidelines the use of quality-adjusted life years (QALYs) is preferred as a measure of outcome since is a measure of life expectancy, weighted by a health-related quality of life. Quality of life is expressed in a utility score, ranging from 0 to 1, where 0 represents death and 1 represents perfect health. This type of a cost-effectiveness analysis is called a cost-utility analysis. The advantage of using such a generic outcome is that it enables policy makers to make comparisons across different interventions and health states. In a cost-utility analysis the incremental costs per year spent in perfect health is calculated.
It is recommended that economic evaluation studies are performed from a broad societal perspective, including all relevant costs and health effects. With regard to costs these can be made both inside and outside the health care sector. Costs that can arise outside the healthcare sector are for instance productivity costs, costs of informal care and costs of over-the-counter medication. With regard to the relevant health effects societal perspective implies the use of a valuation of perfect health and different health states by the general public and not by patients.

Aims and outline of the thesis

The general objective of this thesis is to evaluate the effects of tinnitus on health-related quality of life and costs. Furthermore, the effects of a specialized, stepped-care cognitive behavioral treatment were compared to care as usual. Chapter 1 to 4 were based on data from a randomized controlled trial. Chapter 5 and 6 were based on a study using the ESM to measure (aspects of) HRQOL in daily life.

Chapter 1 describes the differences between the two most frequently used utility measures in economic analysis, the EuroQol-5D and the Health Utilities Index Mark III, in a Dutch population with tinnitus. Utility scores derived from both measures is examined to determine agreement, construct validity and responsiveness.

In Chapter 2 the costs of tinnitus in the Netherlands is examined from a healthcare perspective and a societal perspective. In addition, the impact of both disease and demographic characteristics on the total healthcare and societal costs are investigated.

Chapter 3 aims to assess the effectiveness of a specialized, stepped-care cognitive behavioral approach with elements from tinnitus retraining therapy compared with care as usual. Primary outcomes are health-related quality of life, tinnitus severity and tinnitus impairment.

In Chapter 4 is assessed whether a specialized, stepped-care cognitive behavioral approach is cost-effective as compared to care as usual from a societal perspective. The primary effect parameter in the economic evaluation is the QALY, which is based on health state utilities measured with the Health Utilities Index Mark III (HUI). Costs in the analysis include healthcare costs, patient and family costs, and indirect costs.

In Chapter 5, the use of new methodology in measuring quality of life for use in economic evaluations is examined. The objective of this chapter is to use the Experience Sampling Method to explore the value of obtaining momentary, instead of retrospective, accounts of the description and valuation of person's own HRQOL.

In Chapter 6 the results of the Experience Sampling Method investigating the impact of tinnitus on daily life, are described. The objective of this study is to compare emotions, activities and social interactions in daily life of patients with tinnitus with a non-tinnitus control group.

Finally, the Summary and Discussion provides a general summary and discussion of the main findings. Methodological issues and the implications of the findings for (clinical) practice and future directions are evaluated.

CHAPTER 1

Assessment of health state in patients with tinnitus: a comparison of the EQ-5D and HUI Mark III

Iris H.L. Maes, Manuela A. Joore, Rilana F.F. Cima,
Johannes W. Vlaeyen, Lucien J.C. Anteunis

Published in Ear & Hearing 2011; 32(4); 428-435

Abstract

Objectives Expressing the outcomes of treatment in quality-adjusted life years (QALYs) is increasingly important as a tool to aid decision-makers concerning the allocation of scarce resources within the healthcare sector. A QALY is a measure of life expectancy, weighted by health-related quality of life. These weights are referred to as utility scores and are usually measured by multi-attribute utility measures. Several studies found that different utility measures provide different estimates of the same person's level of utility. The aim of this study was to investigate which of two widely used utility measures, the EQ-5D and the HUI Mark III, is preferred in a tinnitus population

Methods Baseline and follow-up data on EQ-5D and HUI Mark III of 429 patients of a randomized controlled clinical trial, investigating cost-effectiveness of usual care versus specialized care of tinnitus, were included. Agreement, discriminative power, and responsiveness of the health state description and the utility scores were examined.

Results Corresponding dimensions of the EQ-5D and HUI Mark III showed large correlations; although ceiling effects were more frequently observed in the EQ-5D. Mean utility scores for EQ-5D (0.77; SD=0.22) and HUI Mark III (0.64; SD=0.28) were significantly different (Wilcoxon Signed Ranks Test, P-value <0,001), agreement was low to moderate (ICC=0.53). Both health state description and utility scores of both measures discriminated between different severity groups. These groups were based on baseline scores of the Tinnitus Questionnaire. The HUI Mark III had a higher ability than the EQ-5D to detect improved patients from randomly selected pairs of improved and unimproved patients.

Conclusion This study shows that different utility measures lead to different health state descriptions and utility scores among tinnitus patients. However, both measures are capable of discriminating between clinically different groups. The HUI Mark III is more responsive than the EQ-5D, and therefore preferred in a tinnitus population.

Keywords: Tinnitus, outcome assessment, questionnaires, health-related quality of life.

Introduction

Economic evaluation of health care is becoming increasingly important as a tool to aid decision-makers concerning the allocation of scarce resources within the healthcare sector. To make a comparison between different conditions there is a need to express the effectiveness of treatments in terms of quality-adjusted life years (QALYs). A QALY is a measure of life expectancy, weighted by health-related quality of life. These weights are referred to as utility scores. Utilities are mostly determined indirectly, by using quality of life measures with pre-existing utility weights that can be attached to each permutation of responses. Unfortunately, the available multi-attribute utility measures, such as the EuroQol-5D (EQ-5D) and the Health Utilities Index Mark III (HUI Mark III), differ in the conceptualization and operationalization of health, and the valuation method upon which the utility scores are based. Several studies found that these two widely used multi-attribute utility measures, provide different estimates of the same person's level of utility (Barton et al., 2008; Brazier et al., 2004; Espallargues et al., 2005; Feeny et al., 2004; Grieve et al., 2008; Grutters et al., 2007; Hatoum et al., 2004; Marra et al., 2004; Marra et al., 2005).

As a result, these differences can lead to variations in the estimates of utilities and QALYs used in economic evaluations. The purpose of this study was to investigate systematic differences in health state descriptions and utility values obtained with the EQ-5D and the HUI Mark III in tinnitus patients. Subjective tinnitus is the involuntary perception of the concept of a sound without the presence of an external source. It is a chronic condition that is highly prevalent, especially among hearing impaired individuals. Studies show a prevalence of 10% to 20% in the general population, (Davies & Rafie, 2000). Among hearing impaired individuals prevalence has been estimated at 75% to 80% (Adams et al., 1999). Among severe sufferers tinnitus causes affective problems, major declines in concentration, sleeping difficulties, exhaustion and problems in (re-)directing attention (El Refaie et al., 2004; Erlandsson & Hallberg, 2000; Jastreboff et al., 1996; Kroner-Herwig et al., 2003; Scott et al., 1990). These problems have detrimental effects on many areas of functioning, leading to a diminished quality of life.

The aim of the current study was to determine which utility measure is preferred in a tinnitus population. To determine this we will assess agreement and compare the discriminative power and responsiveness of both measures. Moreover, we will investigate the differences between the descriptive system and the utility scores of the EQ-5D and the HUI Mark III. The paper is structured as follows. First, we will introduce the dataset that was used. Next we describe the EQ-5D and HUI Mark III instruments and the analyses we performed. In the results section we compare agreement, discriminative power and responsiveness, for the health state description and the utility scores, of both instruments.

Methods

Measures

The EQ-5D consists of a visual analogue scale and five questions, each representing a dimension of health-related quality of life: mobility, self-care, daily activities, pain/discomfort and anxiety/depression (The EuroQol Group, 1990). The visual analogue scale ranges from best (100) to worst (0) imaginable health state. On this scale patients have to rate their own health state. The five questions have three response levels, which classify the severity of complaints on that specific dimension. The combination of levels over dimensions defines a universe of 243 unique health states (= 3 x 3 x 3 x 3 x 3). To determine an additive scoring function based on these different health states, Dolan (1997) derived preferences for these health states using a time trade-off task in a representative sample of the UK population of 2.997 respondents. In the time trade-off task the respondents were asked to choose between remaining in a state of ill health for a period of time A, or being restored to perfect health for

a shorter period of time B. The utility of the ill health state equals B divided by A. The possible utility scores of the EQ-5D range from –0.59 to 1.0.
The HUI Mark III consists of 17 questions which are used to compute 8 dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/complaints. Each question has five or six levels and 972.000 possible health states can be formed by the levels of the different dimensions. A multiplicative utility scoring function was determined by deriving preferences from a standard gamble task and a visual analogue scale in a random sample of the Canadian general population of 504 respondents. In the standard gamble, respondents are asked to choose between two alternatives: remaining in a state of ill health for sure, or an intervention with two possible outcomes, either restoring perfect health (p) or die immediately (1-p). The risk a respondent is willing to take (p) represents their utility score. Possible utility scores range from –0.36 to 1.00 for the HUI Mark III (Feeny et al., 2002) .
Differences between both measures may arise as a consequence of a difference in the conceptualization and the operationalization of health, and a difference in the scoring algorithm to calculate utilities. The EQ-5D conceptualizes health as an overall construct containing physical, mental, and social functioning (Brooks, 1996), while the HUI Mark III focuses on health 'within the skin', meaning that it purely focuses on the underlying level of impairment (Feeny et al., 1995). Also, the operationalization of health differs between the measures. The EQ-5D has a dimension focusing on the quality of the performance of daily activities, which the HUI Mark III has not. The HUI Mark III contains dimensions that are not present in the EQ-5D: vision, hearing, cognition and dexterity. Especially the hearing and cognition dimensions are likely to be relevant in a population with tinnitus. Furthermore, the answering scales differ. The EQ-5D has three answering levels for each item, while the HUI Mark III has 5 or 6 answering levels. Moreover, the answering scales are defined differently. The EQ-5D levels are defined as: no problems, moderate problems or severe problems. The HUI Mark III levels provide some explanation about what sort of complaints are associated with mild, moderate or severe problems.
The scoring algorithm of both measures were derived using different methods. The EQ-5D UK tariff is based on time trade-off values, while the HUI Mark III scoring algorithm is based on standard gamble and visual analogue scale scores. It is described that the standard gamble leads to higher utility scores than the time trade-off, and the time trade-off leads to higher utility scores than the visual analogue scale (Drummond et al., 2005). Also, the scoring algorithms were derived in different countries (UK versus Canada). Different cultures may value health in different ways (Knies et al., 2009).
The Tinnitus Questionnaire (TQ) (McCombe et al., 2001) is a measure of tinnitus-related distress and will serve as an external anchor to determine discriminative power and external responsiveness of the EQ-5D and HUI Mark III. Based on the scores of the TQ patients can be classified into three different severity classes: mild tinnitus complaints, moderate tinnitus complaints and severe tinnitus complaints.

Study population and data collection

Data were collected as part of a ongoing randomized controlled trial investigating the effectiveness and cost-effectiveness of an integral multidisciplinary treatment for tinnitus versus care as usual (Cima et al., 2009). All patients referred to the centre of audiology and communication (Adelante, Hoensbroek) because of tinnitus complaints, were included. Exclusion criteria were age (< 18 years) and not being able to read and write in Dutch.
The EQ-5D, HUI Mark III and the TQ were administered four times during a twelve month period. At baseline (T0), all questionnaires were administered and completed during the first visit at the Audiological Centre. Respondents were assisted by a trained interviewer if requested. Three (T1), eight (T2) and twelve months (T3) after baseline, the patients were

given access to an internet based electronic environment to complete the battery of tests online. If patients were not able to complete the questionnaire online, a paper version was provided. The present study includes only patients who had fully completed both questionnaires at baseline and after three months. In the first three months, the intervention focused on audiological rehabilitation (hearing aids, sound generators) and counseling.

Agreement

First, agreement in the health state descriptions obtained with the EQ-5D and HUI Mark III were determined by computing frequency tables of the responses on the different dimensions of both measures. Kendall's tau was computed to determine the correlation between the corresponding dimensions of the measures: mobility (EQ-5D) and ambulation (HUI Mark III), pain/complaints (EQ-5D) and pain (HUI Mark III) and anxiety/depression (EQ-5D) and emotion (HUI Mark III). Correlations were interpreted according to the following benchmarks: 0.1 to 0.3 was interpreted as small, 0.3 to 0.5 as medium and >0.5 as large (Cohen, 1988). Ceiling and floor effects of the EQ-5D and HUI Mark III were studied by calculating the proportion of patients with either the best or worst health state description. For patients with a ceiling effect on the EQ-5D, the responses on the dimensions of the HUI Mark III were presented in a frequency table.

To assess agreement between the health state utilities of both measures, a Wilcoxon Signed Rank test and a paired samples t-test were used. Utility scores were tested for normality with a Kolmogorov-Smirnov test. The Intra-class Correlation Coefficient (ICC) was computed based on a two-way mixed effect model, such that the subject effect was random and the instrument effect was fixed. Computations were performed at the individual patient level. An ICC below 0.75 implies poor to moderate agreement; above 0.75 implies good agreement (Gross-Protney & Watkins, 1993). Furthermore, Bland-Altman plots (BAP) were computed with the difference between the utility scores from the EQ-5D and the HUI Mark III on the Y-axis and the mean of the utility scores on both measures on the X-axis. All these analyses were performed on the baseline data.

Discriminative power

Since there is also no gold standard for measuring health state utility, construct validity is usually determined by the discriminative power between clinically different groups. To determine the discriminative power of the health state descriptions of the EQ-5D and the HUI Mark III, the frequencies of responses on the different dimensions were computed in clinically different groups based on TQ baseline scores. A score below 30 on the TQ indicates mild tinnitus, a score between 31 and 46 indicates moderate tinnitus and a score above 47 indicates severe tinnitus. The discriminative power of the utility scores of the measures was determined by calculating the mean utility scores for these groups. Differences in mean scores were tested using ANOVA or the Kruskal-Wallis Test, depending on the distribution of the data.

Responsiveness

First, frequency tables of the health state descriptions of both measures were computed for patients who improved and patients who did not improve. Patients were classified as improved if the score on the TQ dropped 10 or more points from baseline to three months.

Second, the health state utility scores were tested for internal and external responsiveness. Internal responsiveness is a distribution-based method that characterizes the ability of a measure to change over a particular pre-specified time frame. External responsiveness is an anchor-based method that describes the relationship between change in a measurement and change in a reference measurement of health. The two most frequently used methods for

determining internal responsiveness are the effect size (ES) and the standardized response mean (SRM) (Terwee et al., 2003). Effect size is calculated as the change in score divided by the standard deviation of scores at baseline. The standardized response mean is the change in score divided by the standard deviation of the change in score. Both the ES and the SRM were computed for those patients who improved and for patients who did not improve from baseline to three months. They were interpreted using benchmarks for effect size: 0.20 through 0.49 is interpreted as small, 0.50 through 0.79 as moderate and ≥ 0.80 as large (Cohen, 1988). External responsiveness was determined by a Receiver Operating Curve (ROC), which determined how successfully a given score on the EQ-5D or the HUI Mark III could discriminate patients who improved from those who did not improve. Improvement was defined as a decrease in the score on the TQ of 10 or more points and was the state variable. Test variables were the difference scores of the EQ-5D and the HUI Mark III between baseline and the different follow-up measurements. The area under the ROC curve was interpreted as the probability of correctly identifying the improved patient from randomly selected pairs of improved and unimproved patients.

Results

Study population

Of the 429 patients included in the study, 428 completed the EQ-5D and the HUI Mark III at baseline. Patients had a mean age of 54 years and 62.2% were male. The mean hearing loss over the frequencies of 1000, 2000 and 4000 Hertz was 31.50 (17.9). Not all patients completed the follow-up measurement at three months yet. The analyses of responsiveness in this paper are based on the 319 patients who fully completed the EQ-5D and the HUI Mark III at baseline and three months follow-up. Patient characteristics are displayed in Table 1.

Table 1. Characteristics of the study population

Characteristics	Baseline	3 months follow-up
N	428	319
Age		
Mean age in years (SD)	54.3 (11.8)	54.9 (11.4)
Range	20-85	20-85
Gender		
Male (%)	267 (62.2%)	203 (63.6%)
Living situation		
Living alone	85 (19.8%)	62 (19.4%)
Living together	343 (80.2%)	257 (80.6%)
Mean PTT at 1, 2 & 4 kHz (in dB)		
Right	30.0	30.8
Left	31.0	32.4
Overall	31.5	31.8
Duration of tinnitus complaints		
< 1 year (%)	126 (29.4%)	92 (28.8%)
1-5 years (%)	167 (39.0%)	122 (38.2%)
5-10 years (%)	60 (14.0%)	46 (14.5%)
> 10 years (%)	75 (17.6%)	59 (18.5%)

SD = Standard Deviation; PTT = Pure Tone Treshold; dB = decibel

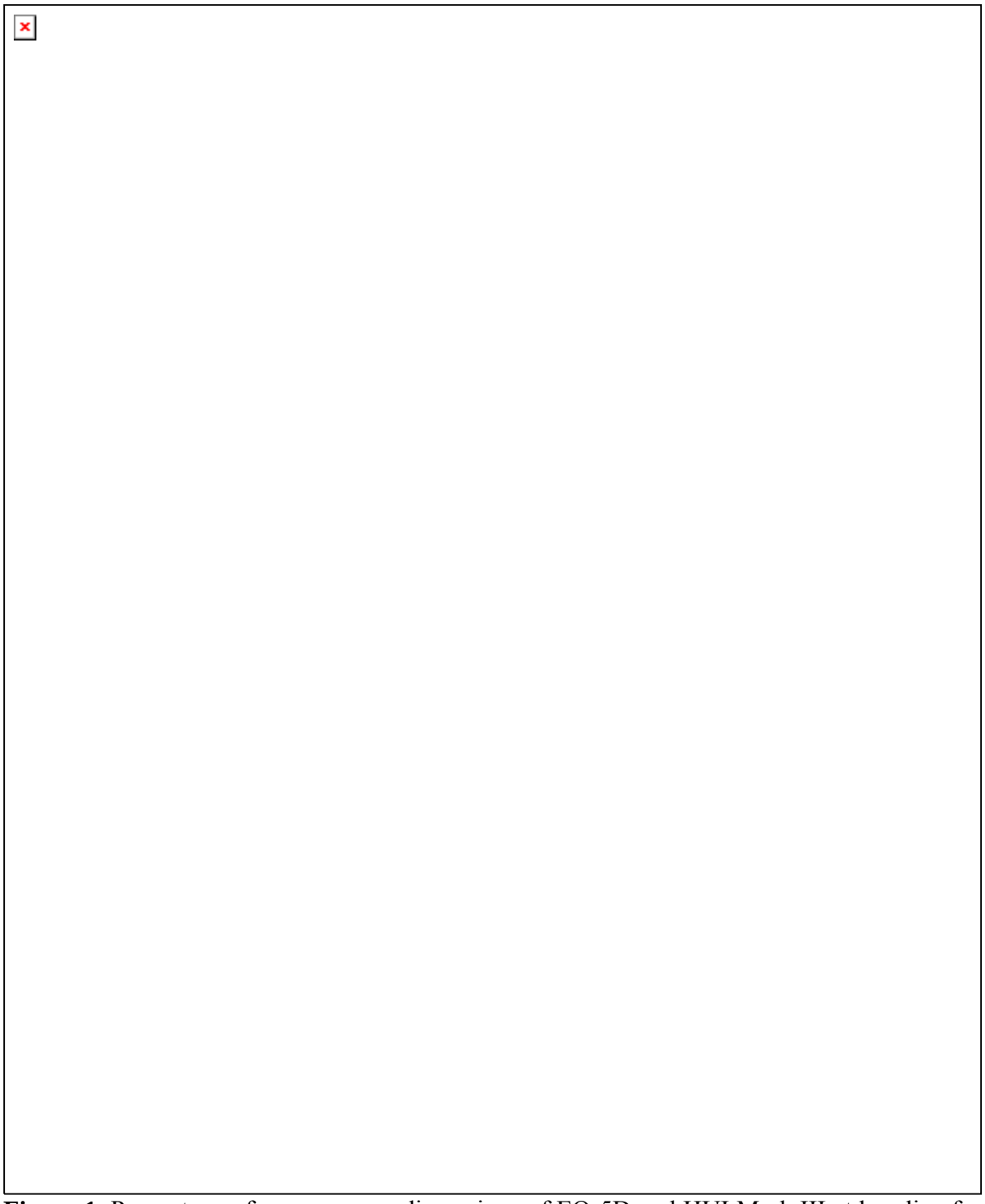


Figure 1. Percentage of responses on dimensions of EQ-5D and HUI Mark III at baseline for mild (N=81), moderate (N=112) and severe (N=235) tinnitus and the total group (N=428).

Agreement

The frequency tables in Figure 1 show most patients had complaints on the dimensions pain/complaints, anxiety/depression and daily activities of the EQ-5D. For the HUI Mark III most patients had complaints in the pain, emotion, cognition and hearing dimension (Fig. 1). With regard to vision, the HUI Mark III shows that approximately 80% of the patients wear glasses. There were large positive correlations (Kendall's tau > 0.50) between mobility (EQ-

5D) and ambulation (HUI Mark III) (Kendall's tau = 0.595) and anxiety/depression (EQ- 5D) and emotion (HUI Mark III) (Kendall's tau = 0.527). There was a moderate correlation between pain/complaints (EQ-5D) and pain (HUI Mark III) (Kendall's tau = 0.487). In both measures floor effects were not observed. Ceiling effects were more frequent in the EQ-5D health state descriptions. The frequency table of Figure 2 shows that patients with a ceiling effect on the EQ-5D report most problems on dimensions that are only present in the HUI Mark III, such as hearing and cognition. However, they also show some problems on HUI Mark III dimensions that correspond with EQ-5D dimensions, such as emotion and pain.
Both the EQ-5D and the HUI Mark III utility scores were not normally distributed (P-value<0.001). The mean utility score for HUI Mark III was 0.64 and the mean utility score for the EQ-5D was 0.77. The utility scores were significantly different distributed (Wilcoxon Signed Ranks test, P-value<0.001). The intra-class correlation coefficient for agreement was 0.53 (95% CI: 0.45; 0.60), which implies a poor to moderate agreement. Bland-Altman plots (Fig. 3) show that the difference between the EQ-5D and HUI Mark III utility scores are larger when the mean utility scores of both measures increases. Furthermore it shows that the HUI Mark III overall has lower utility scores than the EQ-5D.

Figure *2.* Ceiling effects of EQ-5D. Distribution of responses (%) on the HUI Mark III dimensions for those with EQ-5D = 11111 (N=108).

Construct validity

Patients were divided into three clinically different groups based on the TQ scores. These showed that 81 patients (19%) had mild tinnitus complaints, 112 (26%) patients had moderate tinnitus complaints and 235 (55%) patients had severe tinnitus complaints at baseline. A one-way analysis of variance showed that there were no differences between these groups with regard to age, sex or hearing loss.

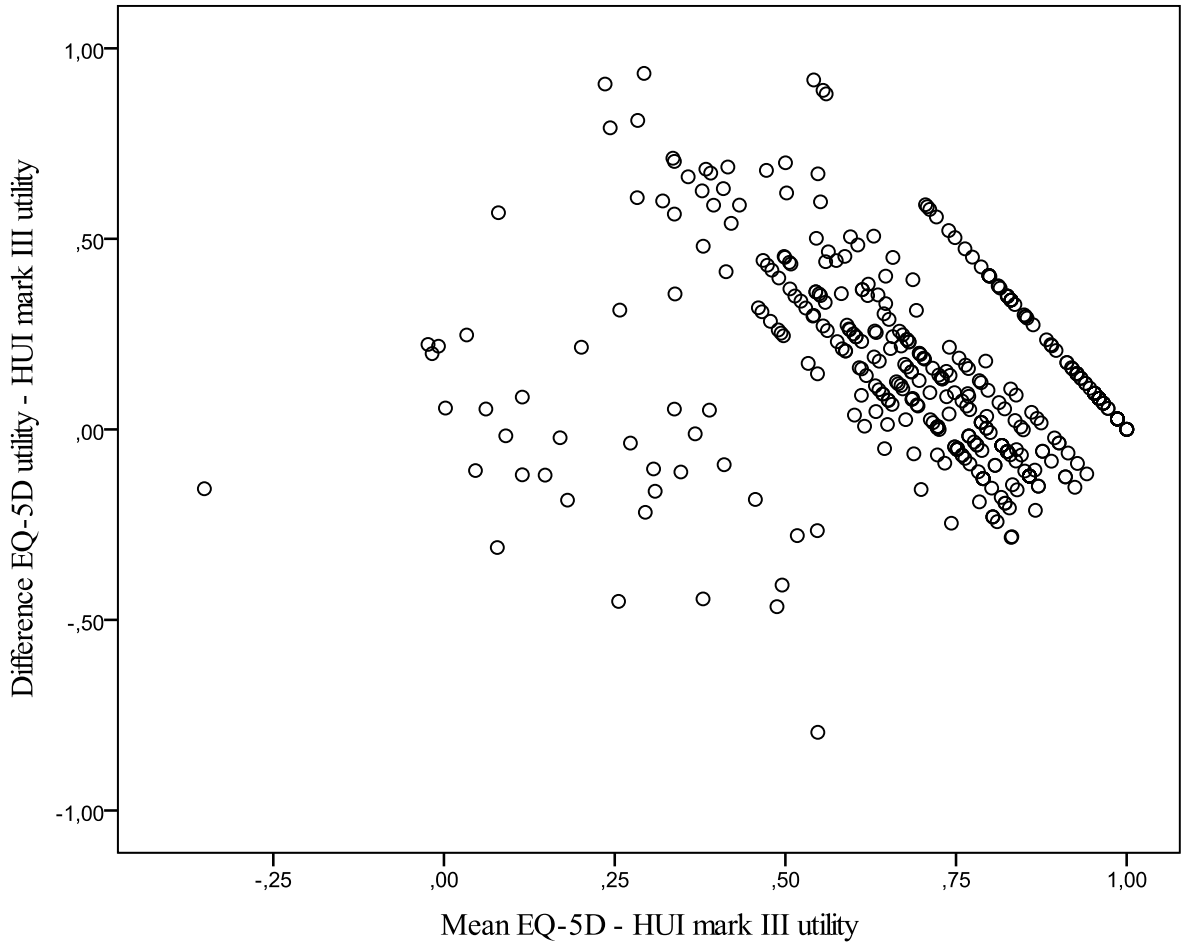


Figure 3. Bland-Altman plot of EQ-5D utility score versus HUI Mark III utility score (N= 428).

With regard to the EQ-5D, the daily activities and the anxiety/depression dimensions distinguish best between mild, moderate and severe groups, with more complaints in groups with more severe tinnitus (see fig 1). The mobility and pain/complaints dimension also distinguish between the different severity groups. The EQ-5D self-care dimension shows no complaints in the mild and moderate groups and some complaints in the severe group. With regard to the HUI Mark III the dimensions hearing, cognition, emotion and pain distinguish between groups with mild, moderate and severe tinnitus. In the other dimensions patients report little or no complaints. Table 2 provides an overview of the mean utility scores for the different clinical groups as measured by the EQ-5D and the HUI Mark III. Both utility measures discriminate between clinically different groups (ANOVA P-value<0.001; Kruskal-Wallis test P-value<0.001). Groups with more severe tinnitus had significantly lower mean utility scores at both baseline and after three months.

Table 2. Mean utility scores for EQ-5D and HUI Mark III

		Baseline				Three months follow-up			
	TQ	N	% ceiling effect	Mean* (SD)	Median**	N	% ceiling effect	Mean* (SD)	Median**
EQ-5D	Mild	81	43.2%	0.87 (.15)	0.79	55	47.3%	0.86 (.16)	0.81
	Moderate	112	33.9%	0.82 (.17)	0.80	86	38.4%	0.84 (.18)	0.80
	Severe	235	14.9%	0.71 (.24)	0.76	178	16.3%	0.71 (.25)	0.73
	Total	*428*	*25.2%*	*0.77 (.22)*	*0.80*	*319*	*27.6%*	*0.77 (.23)*	*0.80*
HUI Mark III	Mild	81	6.2%	0.79 (.18)	0.85	55	1.8%	0.88 (.18)	0.84
	Moderate	112	2.7%	0.82 (.17)	0.78	86	2.3%	0.73 (.24)	0.79
	Severe	235	0.4%	0.55 (.30)	0.55	178	1.1%	0.54 (.30)	0.58
	Total	*428*	*2.1%*	*0.64 (.28)*	*0.70*	*319*	*1.6%*	*0.63 (.28)*	*0.70*

* All statistically significant, ANOVA p<.001

** All statistically significant Kruskal Wallis test, p<.001

Responsiveness

From baseline to three months, 112 patients improved at least 10 points on the TQ, 207 patients showed no improvement. Figure 4 shows that after three months there were slightly less complaints on each of the dimensions of the EQ-5D. In the HUI Mark III dimensions, patients have fewer complaints on the pain, emotion and cognition dimension. With regard to the hearing dimension, patients show more complaints. There were no changes in complaints on the dimensions of the EQ-5D in patients that did not show improvement in the first three months. In the HUI Mark III this group showed slightly more complaints on the hearing, emotion and cognition dimension.

The mean change in utility scores in patients who did not improve on the TQ was not statistically significant for the EQ-5D or the HUI Mark III. The mean change in utility scores for improved patients from baseline to three months was statistically significant for the both HUI Mark III (Wilcoxon Signed Ranks test, P-value<.01) and the EQ-5D (Wilcoxon Signed Ranks test, P-value<.05). The effect sizes of the change in health state utilities from baseline to three months were 0.19 (SD=0.84) for the EQ-5D and 0.21 (SD=0.75) for the HUI Mark III. The SRM of the change in score from baseline to three months was 0.22 (SD=0.94) for the EQ-5D and 0.25 (SD=0.97) for the HUI Mark III. Although all these effect sizes are small, the HUI Mark III is slightly more responsive than the EQ-5D in patients with tinnitus. With regard to the external responsiveness the area under the curve was 0.61 for the HUI Mark III and 0.58 for the EQ-5D (Fig. 5).

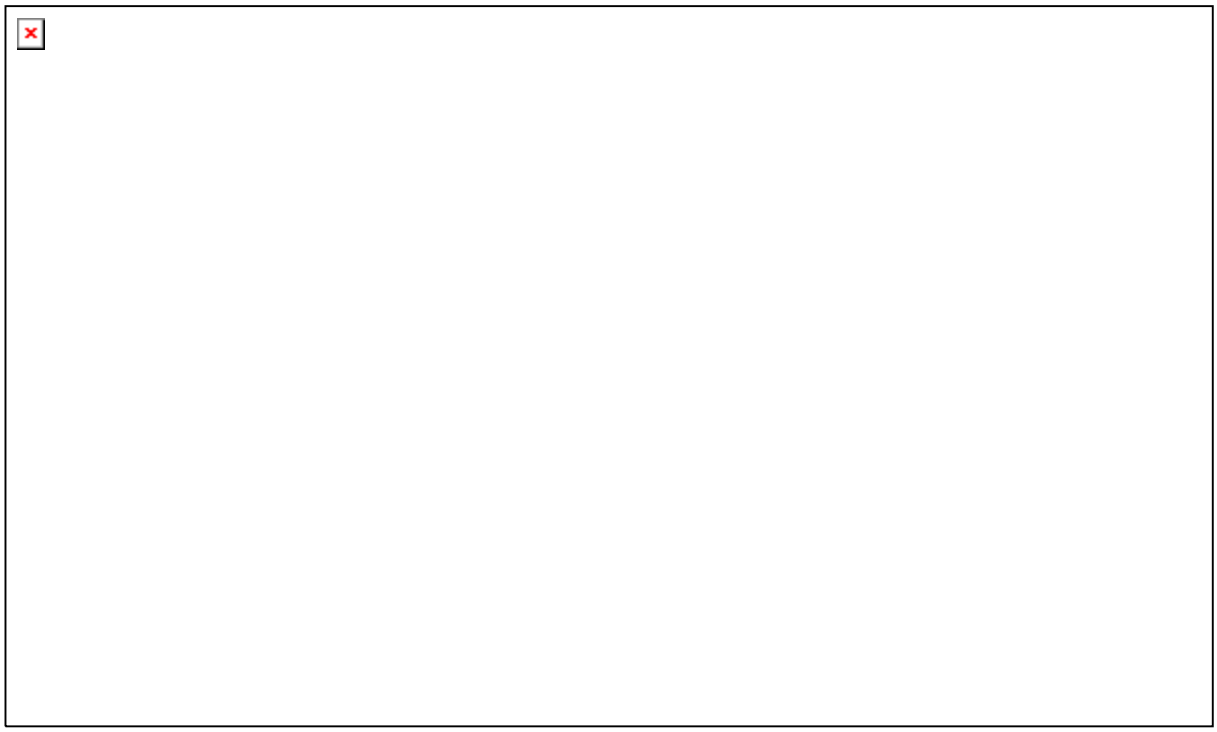


Figure 4. Frequency of dimensions of EQ-5D of patients who improved from T0 to T1 (N= 112)

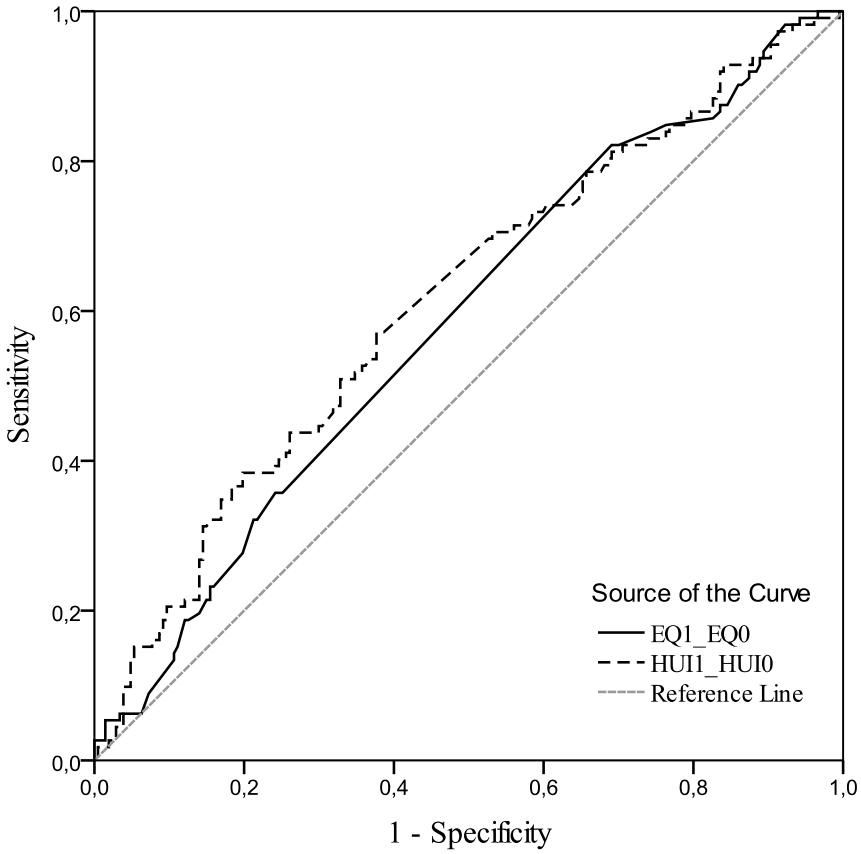


Figure 5. External responsiveness of EQ-5D and HUI Mark III from baseline to three months (N= 319)

Discussion

We investigated agreement, construct validity and internal and external responsiveness of the health state description and utility scores based on the EQ-5D and the HUI Mark III in patients with tinnitus. The results of this study provide insight into the differences between the two widely used utility measures, in patients with tinnitus. Our main findings are the following.

First, although corresponding dimensions showed large correlations, in the EQ-5D health state description ceiling effects were much more frequently observed. Ceiling effects of the EQ-5D are already reported in other studies (Luo et al., 2009; Grutters et al., 2007; Bharmal & Thomas, 2006). Because of the presence of these ceiling effect, it was suggested not to use the EQ-5D in relatively healthy populations (Kopec & Willison, 2003). Patients with perfect health according to the EQ-5D, reported substantial problems on both corresponding as non-corresponding dimensions of the HUI Mark III. From this, we can conclude that both the operationalization of health in items, such as the answering scale used, seem to cause differences between these two measures. It also illustrates one of the disadvantages of the EQ-5D for otherwise healthy populations, but characterized (in part) by a cognitive and/or sensory dysfunction.

Second, the utility scores of the EQ-5D were higher than the utility scores of the HUI Mark III. These findings are in line with the literature (Luo et al., 2009; Grutters et al., 2007; Marra et al., 2005; Oostenbrink et al., 2002). Part of the differences between utility scores can be explained by the differences in health state descriptions, but it is unclear to what amount. Differences could also result from the differences in the utility scoring function. Although in general the time trade-off (used for the EQ-5D) leads to lower scores than the standard gamble (used for the HUI Mark III), the HUI Mark III utility scores were considerably lower than the EQ-5D utility scores in the present study. The utility scoring function of the EQ-5D is additive, assuming no interaction for preferences among attributes at all. The HUI Mark III uses a multiplicative scoring function, with the effect that the level of impairment in one dimension is dependent on the level of impairment in another dimension. The utility scores of the HUI Mark III are expected to be lower, since they take into account the effect of comorbidity.

Third, both measures have discriminative power regarding the health state description. The corresponding dimensions show the most differences between clinically different groups based on severity of the tinnitus. The HUI Mark III also shows a large effect on the hearing and cognition dimension. This is in line with our expectation, since tinnitus is more prevalent in patients with hearing complaints. Furthermore, tinnitus leads to problems in concentration and redirecting attention.

Fourth, health state utility scores of both measures also have discriminative power in groups with more severe tinnitus. These findings are in line with other studies that reported discriminative power of both measures (Fisk et al., 2005; Marra et al., 2004). One study reported discriminative power of only the HUI Mark III (Grutters et al., 2007). In this study the utility scores of the HUI Mark III are lower than the EQ-5D utility scores for each tinnitus severity group.

Fifth, both the EQ-5D and the HUI Mark III show some improvement in the different dimensions from baseline to three months. The HUI Mark III shows more complaints in the hearing dimension. This could be a result of the fact that treatment in the first three months is especially aimed at audiological rehabilitation, drawing their attention to the hearing loss and complaints.

Sixth, the HUI Mark III and the EQ-5D both measured statistically significant change in the mean utility scores of improved patients after the first three months, in which the first level of treatment was finished. In two other studies that compared both measures in a population of

patients with hearing loss, only the HUI Mark III was able to measure statistically significant improvement (Grutters et al., 2007; Barton et al., 2004). An integral multidisciplinary treatment for tinnitus is aimed at improving quality of life, while hearing aid fitting will be most noticeable in the hearing dimension which is only represented in the HUI Mark III. In the present study, the HUI Mark III had a higher ability to detect improved patients, from randomly selected pairs of improved and unimproved patients. A possible explanation for the lack of sensitivity to measure change in the EQ-5D, is the occurrence of a ceiling effect in 25% of the population at baseline. If such a large proportion of patients report perfect health at baseline, it is unlikely to find a considerable utility gain from any intervention.

A shortcoming of this study is the fact that it did not allow us to estimate an instrument order effect. In all subjects the Tinnitus Questionnaire was administered first, followed by the HUI Mark III and the EQ-5D. The extent, to which a change in instrument order would influence differences in the health state description and health state utility, is unknown.

In conclusion, the results on agreement, construct validity and responsiveness show substantial differences between the health descriptions, as well as the utility scores, between the EQ-5D and the HUI Mark III. Differences in conceptualization and operationalization of health explain part of the differences in the utility scores between both measures. It remains unclear how the scoring differences of both measures are responsible for the differences between the utility scores. According to the results of this study, both the EQ-5D and the HUI Mark III can be used in a tinnitus population, although researchers should be aware of the possible ceiling effects of the EQ-5D. This contributes to the evidence that there may not be a superior instrument for measuring health state utility. For now, researchers should use a measurement tool that best fits the condition under investigation. Despite considerable overlap between both measures, we recommend the HUI Mark III as the tool of preference in patients with tinnitus, since it is the most sensitive to change in the condition and is less affected by ceiling effects.

CHAPTER 2

Tinnitus: a cost study

Iris H.L. Maes, Rilana F.F. Cima, Johannes W. Vlaeyen,
Lucien J.C. Anteunis, Manuela A. Joore

Published in Ear & Hearing 2013; 34(4); 508-514

Abstract

Objectives The aim of this study was to examine the costs of tinnitus from a societal perspective. Furthermore, the impact of disease characteristics and demographic characteristics on these costs were examined.

Methods A bottom-up Cost Of Illness (COI) study was performed using the baseline data on a cost-questionnaire of a randomized controlled trial investigating the (cost-)effectiveness of an integral multidisciplinary treatment for tinnitus versus care as usual. Mean yearly costs were multiplied by the prevalence figure of tinnitus for the adult general population in order to estimate the total cost of illness of tinnitus to society. Several questionnaires measuring disease and demographic characteristics were administered. As cost data usually are not normally distributed, a non-parametric bootstrap resampling procedure with 1,000 simulations was performed in Excel to determine statistical uncertainty of the cost estimates per category. The impact of disease characteristics and demographics on costs in patients with tinnitus was investigated using a multivariate regression analyses.

Results Total mean cost of illness was €6,6 billion (95% CI: €1,7 billion - €11,3 billion). The larger part of total COI was not health care related. Total mean healthcare costs were €1,9 billion €0,8 billion - €3,3 billion). The most important predictor of both healthcare costs and societal costs was tinnitus severity. Other significant predictors of higher both healthcare and societal costs were shorter duration of tinnitus and more severe depression as measured with the Hospital Anxiety and Depression Scale. From a societal perspective age was also an important predictor.

Conclusion The economic burden of tinnitus to society is substantial and severity of tinnitus is an important predictor of the costs that patients make.

Keywords: Tinnitus, cost of illness, healthcare costs, societal costs

Introduction

Tinnitus is the perception of a sound for which there is no acoustic source. It is a common chronic health problem of which prevalence has been estimated to be 10-20% in the general population (Andersson, 2002; Davis & El Refaie, 2000). In most cases the symptoms have no identifiable/detectable organic cause and cannot be explained by conventional medical or psychiatric diagnoses. The absence of a known effective treatment often leads to referrals to a variety of caregivers in an unstructured and non-standardized way (Hoare et al., 2010). Patients seek help in various areas of health care, but most of the therapies do not lead to recovery. As a result, tinnitus treatment has been described as fragmentised and costly to both the patients and the society at large (Henry et al., 2005; Lockwood et al., 2002; Reich, 2002). However, empirical evidence supporting this claim is lacking.

To our knowledge, this is the first Cost Of Illness (COI) study for tinnitus. There are two approaches to a COI study: top-down or bottom-up. In a top-down approach the total costs per health care sector in a country are used as a starting point, and fractions of these costs are attributed to a specific disease. However, the use of national health care expenditures may either under or overestimate total direct costs. Also, the exclusion of cost categories that are not included in national health care expenditures (i.e. travel expenses) also biases the estimates of COI since different disease categories may absorb different non-health care costs. Finally, in a top-down COI study all costs are attributed to the primary diagnosis and tinnitus is often not recognized as such. A bottom-up approach in which health care consumption or cost data of a sample of patients are gathered and extrapolated to the total population, is more appropriate in patients with tinnitus.

Although no COI studies have been performed in a tinnitus population, there are several bottom-up studies on costs or health care utilization in patients with other medically unexplained somatic symptoms, like fibromyalgia (Berger et al., 2007; Boonen et al., 2005; Cronan et al., 2002; Robinson et al., 2003; Walen et al., 2001; Wolfe et al., 1997), chronic low back pain (Boonen et al., 2005; Gore et al.) and irritable bowel syndrome (Johansson et al., 2010; Maxion-Bergemann et al., 2006; Nyrop et al., 2007). Boonen et al. (Boonen et al., 2005) found that health care costs and productivity losses are higher in patients with chronic low back pain or fibromyalgia than in patients with a specific inflammatory rheumatic disorder. Studies investigating health care utilization in irritable bowel syndrome revealed that age, comorbidity and severity of symptoms were related to higher health care costs (Johansson et al., 2010; Maxion-Bergemann et al., 2006; Nyrop et al., 2007). In patients with fibromyalgia, illness costs have also shown to be associated with psychological comorbidity, especially depression (Berger et al., 2007; Robinson et al., 2003; Wolfe et al., 1997).

In the present study the costs of tinnitus in the Netherlands were examined from a health care and a societal perspective. In the latter perspective, health care costs, out-of-pocket costs and productivity losses are taken into account. In addition, we investigated the impact of both disease and demographic characteristics on the total health care and societal costs.

Methods

Study Design

This study is part of a randomised controlled clinical trial investigating the effectiveness and cost-effectiveness of an integral multidisciplinary treatment for tinnitus versus care as usual (Cima et al., 2009; Cima et al., 2012). The study population consisted of patients referred to a audiological secondary care facility (Adelante Audiology and Communication, Hoensbroek, the Netherlands) because of their tinnitus complaints. All health care professionals in the surrounding region who have contacts with tinnitus patients were informed on the study. This was done to ensure that the study was easy accessible for all patients. The present study includes only the baseline measurement to ensure that there is no treatment effect on the costs.

Measures

Societal costs associated with tinnitus were measured using a self-administered cost questionnaire with a recall period of three months. We distinguished between three categories of societal costs: health care costs, patient and family costs and indirect costs. Health care costs included contacts with the general practitioner practice, medical specialists in the hospital, care provided by other health care professionals, and medication. The unit costs of all health care costs were adopted from the Dutch guideline for cost research (Hakkaart - van Roijen et al., 2010) unless stated otherwise (Table 2). Whenever necessary, unit costs were converted to the reference year 2009 by means of index numbers. Patient and family costs included e.g. travel expenses, costs of over the counter medication, costs of sports or meditation activities for relieving the tinnitus, the use of ear candles and 'other costs' associated with tinnitus. The cost questionnaire also included the PRODISQ items (Koopmanschap, 2005) to measure loss of productivity (indirect costs). The costs of loss of productivity of paid work were quantified using the human capital approach, which takes into account absence from work as a result of illness, disability or premature death (Drummond et al., 2005). The cost of an hour of productivity loss was based on the mean hourly salary costs for men and women from the Dutch guideline for cost research (Hakkaart - van Roijen et al., 2010).

Tinnitus severity or distress due to the tinnitus was assessed using the Tinnitus Questionnaire (TQ) (McCombe et al., 2001). The TQ consists of 52 items rated on a 3-point scale and assesses the psychological distress associated with the tinnitus. Psychometric properties of the TQ have proven excellent in different languages (Baguley et al., 2000; McCombe et al., 2001). Based on the scores from the Tinnitus Questionnaire, patients were classified into three different severity classes. A TQ score below 30 points was defined as mild tinnitus complaints, a TQ score from 30 to 46 was defined as moderate tinnitus complaints and a TQ score of more than 47 was defined as severe tinnitus complaints.

Anxiety and depressive symptoms were measured with the Hospital Anxiety and Depression Scale (HADS) (Spinhoven et al., 1997), which consists of 14 items that have to be rated from 0='usually' to 4='not at all'. Patients with higher scores have more complaints.

Health-related quality of life was measured with the Health Utilities Index Mark III (HUI Mark III) (Horsman et al., 2003). This is a 17-item questionnaire to assess generic health related quality of life on eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/complaints. A multiplicative utility scoring function can be used to determine a single utility score based on these dimensions. Possible utility scores range from -0.36 to 1.00 (Feeny et al., 2002), with -0.36 being the worst imaginable health state en 1 the best imaginable health state.

In addition, items on general characteristic (age, sex, education), and duration of tinnitus complaints were added to the questionnaire. Duration of tinnitus complaints was scored in one of four categories: < 1 year, 1-5 years, 5-10 years and >10 years. Hearing loss was measured using pure tone audiometry and was defined as the Bilateral Pure Tone Average (BPTA) at 1, 2 and 4 kiloHertz (kHz).

Statistical analysis

The mean costs per three months per patient were multiplied by four to obtain mean yearly costs per patient (van Asselt et al., 2007). Referral by a GP was necessary for seeking treatment in the secondary care setting. In some cases the baseline measurement took place more than three months after the referral to Adelante as a result of a waiting list. Therefore, it was assumed that all patients visited the GP at least once in the year preceding inclusion. For patients who did not report a GP contact in the retrospective cost questionnaire, one GP contact was included in the annual costs. Since inclusion of patients was scattered over three

years, there was no structural seasonal effect in the three months covered by the baseline measurement. Mean annual costs per patient were multiplied by the prevalence figure of tinnitus for the adult general population in order to estimate the total cost of illness of tinnitus to the Dutch society. Approximately 30% of individuals perceive tinnitus at some point in their life and 10–15% experience tinnitus severely enough to seek medical attention (Axelsson & Ringdahl, 1989; Heller, 2003). Earlier studies have shown that 3-5% of the population has severe tinnitus (Davis & El Refaie, 2000; Vesterager, 1997). Since Adelante Audiology and Communication is a secondary care setting, the base case analysis was based on the assumption that our sample is representative for a total prevalence of 10%, with 4% having severe complaints and 6% having mild to moderate complaints. In 2009, the Dutch adult population aged 20 years and older consisted of 12,552,000 residents (Central Bureau of Statistics, 2009). When applying the prevalence rate of 4% severe with severe complaints and 6% with mild to moderate complaints to this population, it can be derived that 539,736 adults had severe tinnitus complaints and 753,120 adults had mild to moderate complaints. The total annual health care costs due to tinnitus were compared with the total health care expenditure in the Netherlands in 2009 (84 billion, (Central Bureau of Statistics, 2009)). Several sensitivity analyses were performed. The first sensitivity analysis shows the impact of varying prevalence rates (5% and 15% instead of 10%). A second sensitivity analysis illustrates the impact of varying the proportion of patients with severe complaints (3% and 5% instead of 4%). A third sensitivity analysis shows the impact of not extrapolating the costs of productivity losses to yearly costs.

To study the impact of tinnitus severity on costs, the patients were classified into three different severity classes based on the scores from the TQ, as described in the previous paragraph. Differences in demographics between these groups were tested with an ANOVA for the continuous variables and a Chi-square test for the categorical variables. All data were tested for normality with a Kolmorgorov-Smirnov test. As cost data usually are not normally distributed, a nonparametric bootstrap resampling procedure with 1,000 simulations was performed in Excel to determine statistical uncertainty of the cost estimates per category (Briggs et al., 1997; Efron & Tibshirani, 1993). The differences in costs between the severity classes were studied by calculating confidence intervals from the bootstrapping procedure. If the 95% bootstrapped confidence intervals (95% BCI) did not overlap, it was concluded that the means were significantly different.

The impact of disease characteristics and demographics on costs in patients with tinnitus was investigated with a multivariate regression analysis. A log transformation was performed on the cost data to resemble normality. Dependent variable was either health care costs or societal costs. Factors that have been tested were tinnitus severity (TQ-score), age, sex, duration of tinnitus complaints, educational level, health-related quality of life (HUI utility score), depression or anxiety (HADS score) and BPTA 1,2,4 kHz. A backward elimination procedure was applied including covariates with $p \leq 0.1$.

Results

Study population

Demographic data of the total group and the different severity groups are shown in Table 1. Patients had a mean age of 54 years and 62.5% were male. The mean BPTA 1,2,4 kHz was 31 dB hearing loss. There were no differences between the groups with regard to age, sex or mean hearing loss. However, there was a significant difference between the groups with regard to the duration of tinnitus complaints ($\chi 2=9.57$; $p=0.04$) and the education level ($\chi 2=36.17$; $p=0.00$). In the group with mild complaints, there were more patients with a high education. In the group with severe complaints there were more patients with a low education.

With regard to duration of tinnitus complaints, in the group with mild complaints there were more patients who had tinnitus complaints for less than a year.

Table 1. Summary of baseline characteristics on the total group and different severity groups based on the scores of the Tinnitus Questionnaire

	Total	**Mild**	**Moderate**	**Severe**	**p***
N	**492**	**96**	**128**	**268**	
Age in yrs (SD)	54,2 (11,5)	54.4 (11.9)	53.9 (11.2)	54.3 (11.6)	0.95
Gender (% male)	62.5	64.6	61.4	61.9	0.87
Education (%)					0.00
Low	45.8	27.1	28.1	44.8	
Middle	27.5	38.6	31.5	29.9	
High	26.7	56.0	25.4	18.7	
Duration (%)					0.05
Less than 1 yr	30.3	36.5	23.6	31.3	
1 to 5 yrs	38.6	27.1	41.7	41.4	
More than 5 yrs	31.0	36.5	34.6	27.2	
BPTA (1, 2, 4 kHZ)	30.8 (17.7)	28.7 (15.6)	29.5 (17.4)	32.3 (18.5)	0.15

*Chi square tests (α= .05) for categorical variables, ANOVA for continuous outcomes

Cost of tinnitus

Table 2 displays the mean annual tinnitus related health care consumption and health care costs. On average, patients visited a health care professional 21.1 times (95% BCI (10.4 – 34.4). Health care professionals that were visited most frequently were the general practitioner, the ENT specialist and the clinical physicist in audiology. The ENT specialist was visited by 54% of the patients and the clinical physicist in audiology by 24% of the patients. All other health care professionals were visited by less than 1% up to 17% of the patients. The total tinnitus related health care costs per patient were €1,544 (95% BCI: €679 - €2,647). The highest health care costs were associated with care by medical specialists (mean cost per patient €771; 95% BCI: €338 - €1,367). Mean costs per patient related to general practitioner care were €225 (95% BCI: €162 – €306). Visits to other health care professionals amounted to mean costs of €527 per patient (95% BCI: €133 – €989). On average patients spent €21 on medication (95% CI: €1 - €46)

Table 1b shows the mean annual out of pocket costs, production losses and societal costs per patient. On average, the out of pocket costs were quite small (€69; 95% CI:), but ranged from €0 to €6,832. Most out of pockets costs were made in the category 'other costs', by 11% of the patients. 'Other costs' were for instance costs of food supplements and alternative therapies (up to €270), head-phones (up to €65), ear protection (up to €170) or sound isolation materials for walls, floors and ceilings (up to €1,500). Patients reported to have been absent from their job as a result of the tinnitus for 15.41 days or 123 hours. Mean annual costs associated with these production losses amounted to €3,702 per patient (95% CI: €520 - €6688) . Mean societal costs per patient were €5,315 (95% CI: €1319 - €9001) per year.

Total mean societal cost of illness of tinnitus in the Dutch population was €6.8 billion (95% CI: €3.9 billion- €10,8 billion). The larger part of total societal cost of illness was not health-care related. Total mean health care costs of tinnitus were € 1.9 billion (95% CI: €1.4 billion - €2.5 billion). This amounts to 2.3% of the total Dutch health care expenditure in 2009.

The results of the sensitivity analyses are shown in figure 1. In the first sensitivity analysis total health care costs range from €1,7 billion to €2.0 billion and the total societal costs range

from €6,4 billion to €7,2 billion. In the second sensitivity analysis, differences in prevalence especially impact on the total societal costs. Depending on different prevalence figures, while the health care costs range from €1.0 billion to €2.9 billion and societal costs range from €3.3 billion to €10.0 billion. In the third sensitivity analysis, productivity losses are not extrapolated to yearly costs. This only impacts on the societal costs that are €3.2 billion in this scenario.

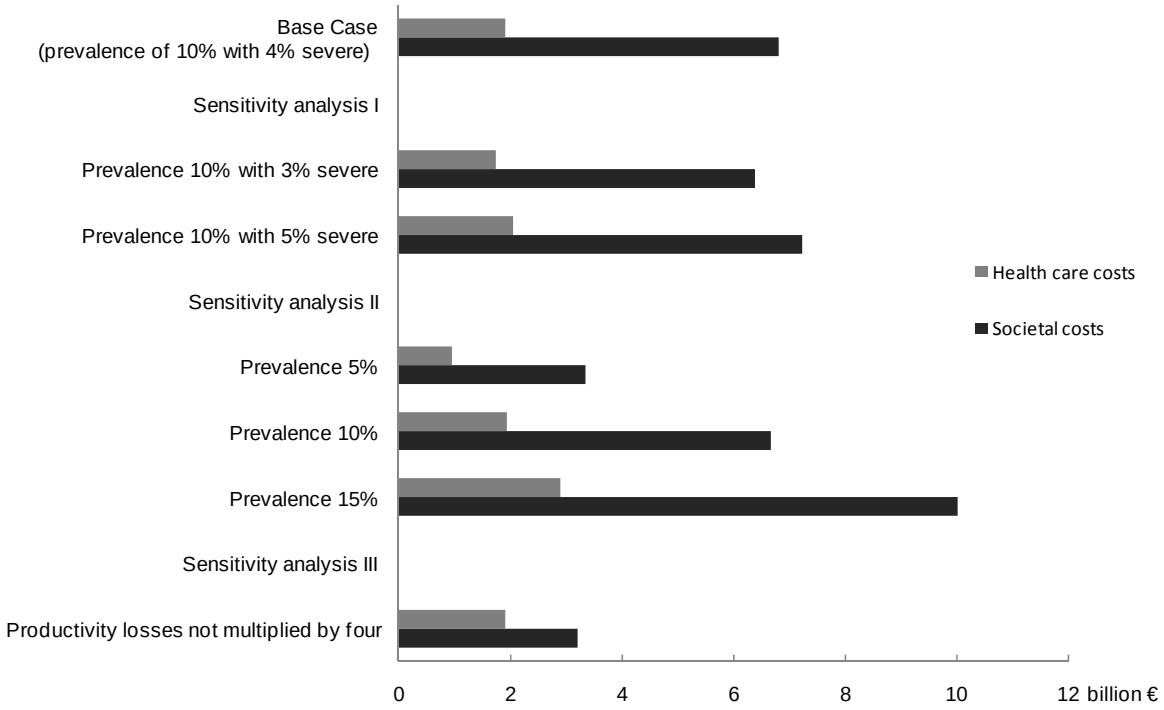


Figure 1. Sensitivity analysis of total cost of tinnitus

The impact of tinnitus severity on costs

Table 2 gives an overview of the total tinnitus related healthcare costs and the costs per discipline for each tinnitus severity group. Although there were slightly more contacts with the general practitioner for the group with severe complaints, no significant differences in the total general practitioner care costs between the three severity groups were observed. Also, there were more contacts with the general practitioner assistant (95% BCI: 0.50 – 1.19 for moderate versus 1.33 – 2.34 for severe) and subsequently this was more costly in the group of patients with the severe complaints (95% BCI: €7 – €17 for moderate versus €19 – €33 for severe). With regard to the care by medical specialists, again the group with severe complaints had more contacts in the hospital and also made more costs compared to the groups with mild and moderate complaints. There were significantly more visits to the ENT specialist and the neurologist in patients with more severe complaints. As a result the mean costs for the ENT specialist (95% BCI: €278– €484 for moderate vs. €524 – €710 for severe) and the neurologist (95% BCI: €8 – €60 for moderate vs. €69 – €237 for severe) were higher for patients with severe complaints. Other healthcare professionals (such as the clinical physicist in audiology, psychologist, physiotherapist and company doctor), were visited more often in the group with moderate and severe complaints than in the group with mild complaints. This resulted in significantly higher mean costs in the group with moderate com-

Table 2. Mean annual costs per patient with mild (N=96), moderate (N=128) and severe tinnitus (N=268)

		Mild		Moderate		Severe		Total	
	Unit costs	**Mean Contacts *BCI***	**Mean Costs *BCI***	**Mean Contacts *BCI***	**Mean Costs *BCI***	**Mean Contacts *BCI***	**Mean Costs *BCI***	**Mean Contacts *BCI***	**Mean Costs *BCI***
Health care costs		11.89	767	20.09	1329	31.38	2218	21.12	1544
		10.0-14.1	*623 - 908*	*15.9 – 24.7*	*1029-1668*	*27.4 – 35.4*	*1912 – 2564*	*10.4 – 34.4*	*679 - 2647*
General practitioner practice		6.20	183	7.27	211	9.88	280	7.78	225
		5.4-7.2	*156 - 213*	*6.1 – 8.8*	*170 - 263*	*8.8 – 11.2*	*247 – 322*	5.5 – 10.8	162 - 306
GP visit	28.00[f]	4.75	133	5.48	153	6.48	181	5.57	156
GP home visit	43.00[f]	.88	37	0.72	31	1.33	57	0.98	42
GP assistant visit	14.00[f]	.50	7	0.82	11	1.78	25	1.03	14.44
GP weekend and evening	59.56[g]	.09	5	0.25	15	0.29	17	0.21	12
Medical specialists		3.08	397	4.33	559	8.06	1039	5.16	771
		2.3 – 4.0	*290 – 510*	*3.0 – 5.9*	*387 – 758*	*6.6 – 9.8*	*849 - 1259*	*2.4 – 9.3*	*338 – 1367*
ENT specialist visit	129.00[f]	2.12	274	2.91	376	4.74	612	3.26	420
Dental surgeon visit	129.00[f]	.04	6	0	0	.18	23	0.07	9
Neurologist visit	129.00[f]	.17	22	0.25	32	1.08	140	0.50	65
Other medical specialist	129.00[f]	.75	96	1.17	151	2.06	265	1.32	171
Other health care professionals		2.36	182	7.55	540	11.37	859	7.10	527
		1.3 – 3.8	*116 – 252*	*5.2 – 10.3*	*392 – 707*	*9.1 – 14.0*	*695 – 1051*	*1.5 – 13.3*	*133 – 989*
Clinical physicist in audiology	145.02[a]	.75	108	.87	127	1.73	251	1.12	162
Physiotherapist	36.00[f]	.89	32	2.62	94	3.17	114	2.23	80
Psychologist	80.00[f]	.00	0	.53	43	1.78	142	0.77	62
Psychiatrist	129.00[f]	.00	0	.28	28	.45	47	0.24	25
Social worker	65.00[f]	.00	0	.03	2	.65	42	0.23	15
Occupational therapist	22.00[f]	.04	1	.03	1	.37	8	0.15	3
Company doctor	129.00[f]	.21	26	.97	126	1.28	165	0.82	106
Homeopath	10.00 – 82.50[h]	.08	4	.78	43	.56	29	0.48	25
Acupuncturist	20.00 – 93.33[h]	.38	10	1.30	71	1.28	59	0.99	47
Haptonomist	12.50 – 40.00[h]	.00	0	.00	0	.00	0	.00	0
Magnetizer / Faith healer	28.00 – 50.00[h]	.00	0	.12	5	.10	1	.08	2

Prescribed medication									
Medication	Various[b]	0.25	5	.93	19	2.07	39	1.08	21

	Unit costs	**% patients Incurring costs**	**Mean Costs *BCI***	**% patients Incurring costs**	**Mean Costs *BCI***	**% patients Incurring costs**	**Mean Costs *BCI***	**% patients Incurring costs**	**Mean Costs *BCI***
Patient and family costs*			31 *8 – 61*		61 *32 – 94*		115 *55 - 186*		69 *12 - 170*
Over the counter medication	Various[h]	5 %	6	9 %	5	10 %	10	6 %	7
Travel expenses*	Various[h]	-	3	-	5	-	10	-	6
Sports	Various[h]	1 %	1	9 %	14	6 %	44	6 %	20
Meditation	Various[h]	1 %	1	6 %	4	3 %	8	3 %	4
Earcandle	Various[h]	0 %	0	1 %	1	1 %	0	1 %	0
Other	Various[h]	8 %	20	13 %	33	12 %	43	11 %	32

		Mean days *BCI***	**Mean Costs *BCI***	**Mean days** *BCI***	**Mean Costs *BCI***	**Mean days** *BCI***	**Mean Costs *BCI***	**Mean days** *BCI***	**Mean Costs *BCI***
Productivity losses	Mean /hour[f]	5.08 *1.5 -10.0*	1222 *360 – 2412*	19.87 *11.2 -30.2*	4781 *2699 – 7266*	21.26 *15.3 – 27.6*	5105 *3679 – 6620*	15.41 *2.2 – 27.8*	3702 *520 – 6688*
Societal costs			2020 *1116 – 3169*		6170 *3917 - 8731*		7438 *5896 -9190*		5315 *1319 - 9001*

BCI = Bootstrapped confidence interval

* For this category only the costs were calculated; ** Based on 8 hour work days

a) Anonymous source; b) GIP databank 2009; c) www.nvab.nl; d) oral communication with several hearing aid dispensers; e) cost calculation; f) Hakkaart et al. 2010; g)www.nza.nl/regelgeving/tarieven; average tariff 2009 calculated for Limburg; h) cost questionnaire.

plaints (€540) compared to mild complaints (€182), but not in the group with severe complaints (€854) compared to moderate complaints (€539). The higher costs are especially the result of patients with more complaints having more contacts with psychologists, social workers and clinical physicists in audiology. Table 2 also shows that although patients with severe complaints on average use more medication than those in the mild and moderate group, this is however not significantly more costly.
In Table 2 the out-of-pocket costs and the productivity losses are shown for each tinnitus severity group. There were no differences between the groups with regard to the overall out-of-pocket costs. However, the mean costs of the travel expenses were higher in the group with severe complaints (95% BCI: €3 – €6 for moderate versus €8 – €11 for severe). Also the group with moderate and severe complaints had more expenses with regard to the use of sports facilities (95% BCI: €4 - €28 and €10 - €98, respectively) for relieving the tinnitus than patients with mild complaints (95% BCI : €0 – €3). Finally, the productivity losses were higher in the group with moderate (€4781; 95% BCI: €2599 - €7266) and severe complaints (€5,105; BCI: €3,679 - €6,620) as compared to the group with mild complaints (€1,222; 95% BCI: €360 - €2,412) because there were more patients on sick leave as a result of the tinnitus in these groups.

The impact of disease characteristics and demographics on costs

The determinants of costs are shown in Table 3. The most important predictor of healthcare costs was tinnitus severity. More severe complaints are significantly related to higher healthcare costs. Other significant predictors of higher healthcare costs were shorter duration of complaints and a more severe depression score on the HADS. With regard to the societal costs severity of tinnitus complaints was the most important predictor. Other significant predictors of higher societal costs were a younger age, shorter duration of complaints and a more severe depression score on the HADS.

Table 3. Results of multivariate regression analysis after backward elimination of covariates with $p \leq 0.1$

Dependent variable	Independent variables	R^2	B	P-value
Healthcare costs (N=409)	Constant	0.27	5.194	.00
	TQ score		.317	.00
	Age		-.102	.02
	Duration (1-5 yrs)		-.215	.00
	Duration (> 5 years yrs)		-.268	.00
	HADS depression		.131	.01
Total costs (N=424)	Constant	0.24	6.790	.00
	TQ score		.197	.00
	Age		-.237	.00
	Duration (1-5 yrs)		-.118	.01
	Duration (> 5 years yrs)		-.213	.00
	HADS depression		.203	.00

TQ=Tinnitus Questionnaire; HADS=Hospital Anxiety and Depression Scale

Discussion

To our knowledge, this is the first study to examine the health care utilization and costs of patients with tinnitus from a societal perspective. Moreover we included an analysis of the impact of demographics and disease characteristics on costs.

With regard to health care utilization, tinnitus sufferers seem to be a heterogeneous group as they seek help in various areas of health care. However, the larger proportion of patients (>50%) seek help in three different caregivers, namely the GP, the ENT specialist and the clinical physicist in audiology. The mean annual health care costs of tinnitus are €1,544 per patient. Literature on other medically unexplained disorders that are comparable to tinnitus in the Netherlands found more or less the same results. The annual costs of fibromyalgia were estimated at €1,311 and the cost of chronic low back pain at €1,104 in 2002 (Boonen et al., 2005). The mean annual productivity costs are €3,702 for patients with tinnitus. These costs are higher than the productivity losses of comparable disorders. The productivity costs of fibromyalgia and CLBP were €2,573 and €2,939 respectively (Boonen et al., 2005).

When applying a prevalence of 10%, with 4% having severe complaints to the Dutch adult population in 2009, mean societal cost of illness was €6,8 billion. Comparing this to the cost of illness of borderline personality disorder in a Dutch population, the costs of tinnitus are 3 times as high. The total societal cost of borderline personality disorder were €2,2 billion in 2000 (van Asselt et al., 2007). The prevalence of borderline personality disorder is 1% which means that the mean costs per patient are considerably higher than in patients with tinnitus (van Asselt et al., 2007). With a prevalence rate of 4.8% the societal costs of social phobia in the Netherlands 2003 were €136 million per million inhabitants, which is approximately €1,7 billion for the total population (Acarturk et al., 2009). A top-down study of low back pain in the Netherlands reported total societal costs of €3,5 billion in 2007 (Lambeek et al.).

Patients with severe complaints had significantly more health care costs than patients with mild and moderate complaints. There were no differences between the groups with regard to out of pocket costs. Productivity losses were significantly higher in the moderate and severe groups than in the mild group. Severity of tinnitus was the most important positive predictor of health care costs. Other significant predictors were duration of complaints, depression scores and age. For societal costs the most important predictor was age. This is probably the result of the fact that almost three quarter of these costs are explained by the losses in productivity. 18% of the patients in this study were 65 or older and therefore had no productivity losses.

The findings of this study are in line with a studies investigating the relation between health care utilization or costs and disease characteristics in other studies (Berger et al., 2007; Johansson et al., 2010; Maxion-Bergemann et al., 2006; Nyrop et al., 2007; Robinson et al., 2003; Walen et al., 2001; Wolfe et al., 1997). Future research could also take into account the relation between income and health care and societal costs. This was not possible in the current study since a substantial proportion of the patients did not provide information on their level of income.

The patient sample here may not be representative of the entire tinnitus population. Therefore extrapolating mean costs per patient to the total population could have led to bias. First, we included patients from a secondary care setting, which could mean that the symptoms these patients experience are more severe than the symptoms of patients that seek help in a primary care setting. However, measures were taken to ensure that the health care facility was easy accessible to all patients. Moreover, it was a large sample (N=492) and a substantial number of patients (N=96) with mild complaints were included in the study. The health care costs range from €1.0 billion to €2.9 billion, and the societal costs range from €3.2 billion to €10.0 billion, depending on the assumption made to extrapolate the costs to the total population. Second, it is possible that costs that are made in the three months previous to the start of

treatment are not representative for the whole preceding year. There were some costs, for instance the costs of sound isolation, that are probably made only once. On the other hand, it could be that other patients also made these costs because of the tinnitus complaints at some point in the preceding year.

Another drawback of the study is the fact that a cost-questionnaire with a recall period of three months was used. It entirely relies on the patient's memory and also on the patient's judgment of what costs are related to the tinnitus and what costs are not. However, a three month recall period is generally thought of as acceptable (Severens et al., 2000; van den Brink et al., 2004) and it was clearly stated to all participants that we were interested in tinnitus-related costs only. Each question contained a remark that the focus was on tinnitus-related costs.

Summarizing the aforementioned findings one can conclude that the economical burden of tinnitus to society is substantial and that severity of tinnitus is an important predictor of the costs that patients make.

CHAPTER 3

Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial

Rilana F.F. Cima, Iris H.L. Maes, Manuela A. Joore, Dyon J.W.M. Scheyen, Amr El Refaie, David M. Baguley, Lucien J.C. Anteunis, Gerard J. van Breukelen, Johannes W. Vlaeyen

Published in The Lancet 2012; 379(9830):1951-9

Abstract

Background Up to 21% of the adult population has at least once in their lifetime been bothered by tinnitus, which is one of the most distressing and debilitating audiological problems. The lack of medical cures and standardized practice often result in costly and prolonged referral trajectories, and unnecessary suffering. A stepped-care approach, with a basic cognitive behavioral therapy program for all patients, and a follow-up approach for patients with more severe tinnitus complaints, is presently investigated.

Methods 741 adults (>18 years) with a primary complaint of tinnitus were assessed for eligibility to enter a randomized controlled trial, comparing Specialist Care (SC) consisting of cognitive behavioral therapy (CBT) with elements of sound-focused tinnitus retraining therapy (TRT) with Usual Care (UC). Primary outcomes were health-related quality of life (HUI), Tinnitus Severity (TQ), and Tinnitus impairment (THI), which were assessed pre-treatment, and at 3, 8 and 12 months after randomization. Multilevel Mixed regression was used for intention to treat analyses; final analysis included all participants for whom we had baseline data on primary and secondary outcomes. This study is registered; number NCT00733044.

Findings 492 patients, blinded for treatment allocation, were randomly assigned to either UC (n=247) or SC (n=245), pre-stratified on tinnitus-severity and hearing impairment, completed baseline measurements, and were included in final analyses. Overall, adjusted mean changes were higher in the SC group than in the UC group at 12 months for HUI (between-group difference=0.059 [95% CI 0.025 -0.094]), TQ (between-group difference=-8.062 [95% CI: -10.829; 5.295]) and THI (between-group difference=-7.506 [95% CI: -10.661; 4.352]), with effect sizes of 0.24, 0.43 and 0.45 (Cohen's d) respectively. Moreover, SC generates greater improvements in general negative emotional states, level of tinnitus-related catastrophic thinking, and tinnitus-related fear than UC. Additionally, the treatment was effective irrespective of initial tinnitus severity levels. No adverse events or harmful side-effects were reported throughout the trial.

Interpretation A specialized CBT-based treatment might be the treatment of choice for milder forms of tinnitus suffering as well as for more severe tinnitus incapacitation, and hence may be considered for widespread implementation.

Introduction

Sixteen to 21% of the adult population is at one point in life bothered by tinnitus (Krog et al., 2010), the perception of a noxious disabling internal sound without an external source. Although often not recognized by the general public, tinnitus is one of the most distressing and debilitating audiological problems, affecting almost all aspects of daily life (Cima, Vlaeyen et al., 2011; Javaheri et al., 2000). Cognitive impairments and negative emotions associated with tinnitus are shown to be most troubling for patients and their families (El Refaie et al., 2004; Hallam et al., 2004).

Since tinnitus is not easily objectified, and medical curative efforts have been unsuccessful, the effective management of tinnitus complaints has been a challenge, requiring a multitude of disciplines and usually prolonged trajectories (Cima et al., 2009). Evidence for a uniformly successful treatment of tinnitus is lacking, and current usual care practices for tinnitus primarily consist of fragmentized interventions; often resulting in communicating to patients that nothing can be done about the tinnitus, but learn to live with it (Cima et al., 2009). The lack of standardized practice presents difficulties in unifying assessment, treatment, identifying subsets of patients with differential clinical demands, and in comparing clinical and research outcomes (Hoare et al., 2010).

Two main tinnitus-treatment approaches can be distinguished. First, sound-based therapies, such as tinnitus retraining therapy (TRT), involve tinnitus-masking methods on the sound-perception-level in combination with structured counseling sessions (Jastreboff & Hazell, 2004; Phillips & McFerran, 2010). This approach, commonly based on Jastreboff's neuro-physiological model (Jastreboff & Hazell, 1993), is aimed at ameliorating tinnitus distress, through education and exposure to a neutral external sound. By habituating tinnitus-patients to this neutral sound, which is hypothesized to generalize to the threatening tinnitus-sound, tinnitus annoyance is expected to diminish. Supporting evidence for the TRT approach is scarce, and most of the published reports derive from retrospective and uncontrolled trials (Hiller & Haerkotter, 2005; Hoare et al., 2010; Phillips & McFerran, 2010). A second main approach is cognitive behavioral therapy (CBT) for tinnitus (Kroner-Herwig et al., 2003; Martinez-Devesa et al., 2010; Zachriat & Kroner-Herwig, 2004). CBT is a more comprehensive form of psychotherapy aimed at modifying dysfunctional beliefs and behaviors. Typically, CBT for tinnitus includes psycho-education, relaxation, exposure-techniques, and behavioral reactivation, often in combination with mindfulness-based training. Although, CBT-based tinnitus-treatment approaches have shown to reduce suffering and improve quality of life, large scale and well-controlled trials are still needed (El Refaie et al., 2004; Hesser et al., 2011; Kroner-Herwig et al., 2003; Martinez-Devesa et al., 2010). The premise that the intensity of CBT-treatment can vary depending on severity of tinnitus-complaints, has never been tested.

We developed a novel multidisciplinary tinnitus-treatment protocol; a stepped-care CBT based approach with elements from TRT. A stepped-care approach is a framework for organizing health services based on individual patients' needs, with a gradual increase in the intensity of the care at each level (Von Korff & Moore, 2001). The main aim of the current study was to investigate the effectiveness of a this new specialized tinnitus-treatment protocol versus care as usual, using a randomized controlled design (Cima et al., 2009).

Methods

Aims and hypotheses

We hypothesized that [a] Specialized care (SC) would be more effective than Usual Care (UC) in increasing generic health-related quality of life, reducing distress caused by the tinnitus, and reducing tinnitus-related impairment, and [b] SC would be more effective than

UC in reducing general negative affect, the level of catastrophic mis-interpretations of tinnitus, and tinnitus-related fear.

Study design

A two group, two-stepped care, single-centre randomized controlled trial was carried out with adult tinnitus patients, with 3 follow-up assessments at 3, 8 and 12 months after randomization (see Appendix B for specifics on data collection). Tinnitus patients referred to our centre were invited for a first off-centre baseline assessment contact, after which they were randomly allocated to either Usual Care (UC) or Specialized Care (SC). The Medical Ethical Board of the Rehabilitation Foundation Limburg reviewed and approved of the study protocol (METC-SRL: 11/09/2006) and trial funding was supported by Netherlands Organization for Health Research and Development (ZonMw; 945-07-715). The trial has been registered at ClinicalTrial.gov (NCT00733044).

Participants

Adult patients referred to our centre with a primary complaint of subjective tinnitus were eligible for inclusion. Patients were excluded when unable to read and write in Dutch, when health problems, such as terminal illness or physical problems impairing travelling to our centre, prevented participation, and when they had undergone treatment at our centre within 5 years prior to trial enrolment. Patients were assessed by an ENT-physician to rule out otological pathology requiring immediate medical care. Informed consent was obtained before assessment and trial-entry; both patients and assessors were blinded for treatment allocation.

Randomization and blinding

Treatment allocation was by randomization, pre-stratified on both tinnitus-severity (stratification cut-off point at 47 points on the tinnitus questionnaire) and hearing impairment (stratification cut-off point at the pure-tone average (PTA) of 60 dB hearing level in worst ear), giving four strata. Within each stratum, patients were randomized to one of both treatment arms in blocks of 4 patients. The randomization procedure was performed by one of the independent research assistants at an off-centre location, after receiving informed consent and baseline assessment.

Patients were blinded for treatment allocation. Prior to trial enrolment patients were informed they would be allocated to one of two different treatments, aimed at tinnitus management, using a client-centered, stepped-care approach. They were also aware that by giving their consent they would not be informed as to which treatment they were allocated to. Early in the intervention-procedure detailed information about the treatment received was unveiled, while the participants remained blind to the content of the alternative treatment.

Intervention-procedures

Systematic review

Panel 1 provides a systematic review on current treatment approaches in tinnitus management. The combination of two main theoretical models and treatment approaches was found to be novel, and not studied before (Cima et al., 2009).

Overview

Both UC and SC were setup in a stepped-care manner (see figure 1). Both step-1 and step-2 in UC and SC were finalized after 8 months followed by a no-contact period of 4 months up until the last follow-up assessment. Step-2 treatment had a duration of 12 weeks maximally in

both UC and SC. Case Report Forms (CRF) were used for each patient to standardize treatments and for trial purposes, replacing the medical charts. Each CRF included extensive protocols for each separate professional, including supporting staff, and for multidisciplinary patient-related activities.

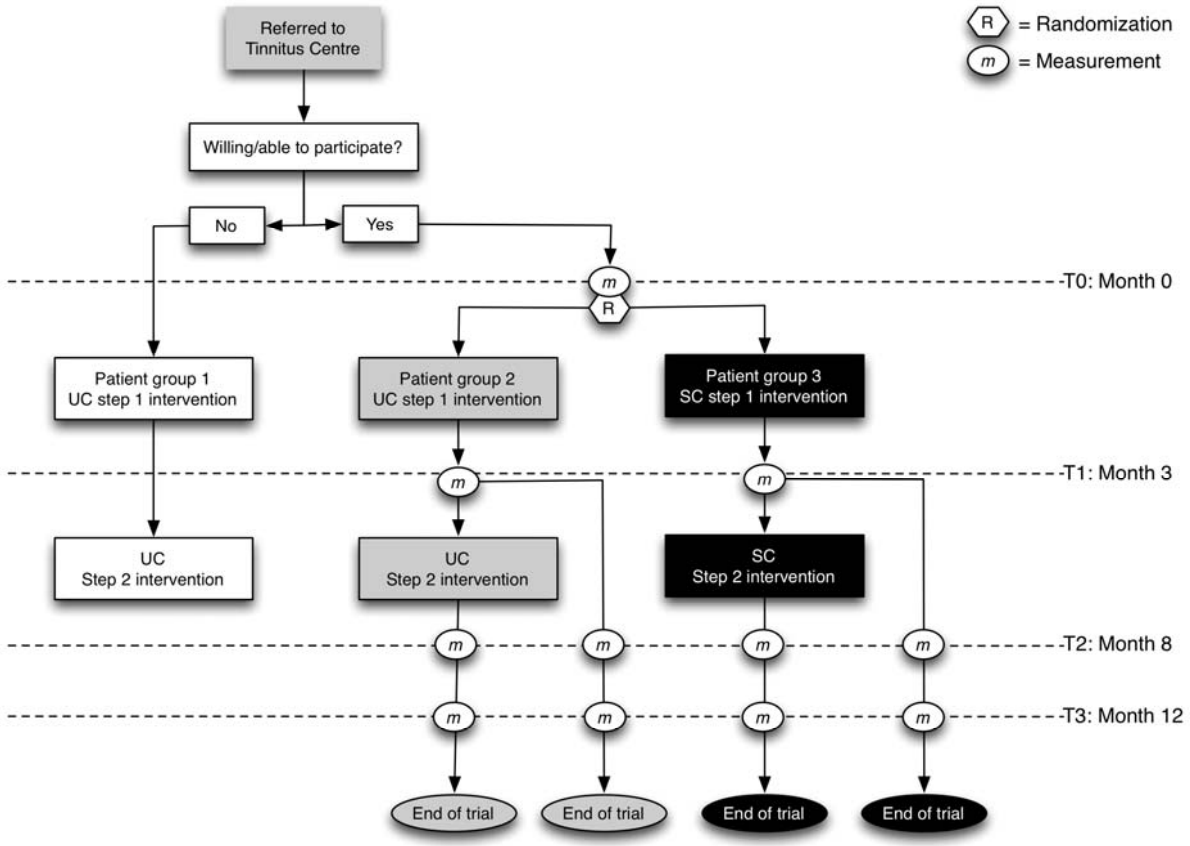


Figure 1. Flowchart

Care as Usual (UC)
The UC procedure entailed a standardized protocol modelled after the average care as is usually provided by secondary-care audiological centres across the Netherlands. A qualitative study was carried out by means of a telephone survey, including all audiological centres (n=26) currently operative in the Netherlands. The number of professionals involved and counseling hours were averaged and discipline-type and healthcare activities were categorized by two independent raters, resulting in the UC treatment protocol (see PANEL 2).
Step-1 of UC treatment consisted of a standard audiological intervention. For patients with mild complaints, treatment ended after the first step, while they remained in the trial for follow-ups. When tinnitus suffering was more severe (as measured at baseline and after audiological counseling), patients entered step-2 treatment.

Specialized Care (SC)
The first step of SC-treatment consisted of multidisciplinary diagnostics and specific TRT-based counseling elements, carried out in a cognitive behavioral framework (including audiological rehabilitation when necessary). For patients with mild complaints this basic intervention was expected to suffice, and they were measured for follow-ups only. When

tinnitus suffering was more severe (as measured at baseline and after psychological screening), patients entered step-2 treatment, which consisted of three 12-week group-treatment options; Program A for patients suffering from tinnitus on a moderate to severe level, Program B for severe tinnitus complaints, and program C for severely hearing impaired tinnitus patients (see PANEL 3).

PANEL 1: Research in Context

Systematic Review

A rather broad range of search terms to include all relevant studies performed on tinnitus and group treatment. All Systematic reviews, reviews, and meta analyses were included as well. *Search terms:* Tinnitus AND Trial AND review (OR management OR care, OR specialized clinic,, OR multidisciplinary, OR therapy, OR treatment, OR systematic, OR meta analysis, OR cognitive behavioral, OR psychological, OR relaxation OR education OR quality of life, OR stress, OR distress, OR coping, OR anxiety, OR depression, OR chronic, OR pain, OR costs, OR cost analysis, OR effects, OR outcome assessment OR sound therapy OR TRT) NOT (Complementary Therapies, OR Acupuncture, OR Ginko biloba, OR surgery, OR pharmacology). It is important to note that he second search term 'Trial' includes studies using other methodological designs than RCT only, this according to the MeSH thesaurus. *Population*: Adult tinnitus population. *Intervention*: Multidisciplinary care, specialized clinic, cognitive behavioral therapy, psychological treatment, relaxation, education, tinnitus retraining, TRT (sound therapy). *Outcome Measures:* Quality of life, stress/distress, depression, anxiety, coping. Tinnitus distress/handicap/impairment. *Methodological filters:* Systematic review, RCT, follow-up of cohort design, case control study. *Databases:* Medline (1980 – present), Psychinfo (1972-present), Psyarticles, Cinahl (1982 – 2005), ERIC database (1966 – 2005/09), Econlit, DARE database, Education Resources Information Centre, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Controlled Trials Register, Cochrane Methodology Register, NHS Economic Evaluation Database, Health Technology Assessment Database, Cochrane Database of Methodology Reviews (CDMR). *Number of manuscripts retrieved***:** After performing the first search strategy described above a total number of 216 manuscripts were retrieved (Medline: 125; Psychinfo: 20; Psyarticles: 3; Cinahl: 14; ERIC: 11; Econlit: 2; DARE: 36; Cochrane: 5). *Validity assessment:* Two independent reviewers assessed all studies for inclusion quality. Included were: systematic reviews, meta analyses, reviews, RCT's and other trials comparing different treatment combinations based on group treatments, including behavioral modification, relaxation, attention diversion and exposure, biofeedback, coping strategies, specific tinnitus management programmes, and multidisciplinary approaches. Not included were studies on pharmacological treatment, complementary or alternative treatments, and studies based on animal-models and neuro-magnetic stimulation. *Results:* The total amount of selected manuscripts was 22, of which 8 systematic reviews, 9 RCT studies, 3 follow-up or case control studies, and 1 controlled but not randomized and 1 evaluation of current practice.

Interpretation

The combination of 2 main theoretical models, and treatment approaches, Cognitive Behavioral Therapy (CBT) and Tinnitus Retraining therapy (TRT) was found to be novel. CBT for tinnitus seems the most promising approach in diminishing tinnitus related distress and decrease main complaints of patients. The use of sound generating devices, whether masking devices, wearable players or hearing aids, even when combined with directive counseling sessions, have of yet not been proven to be effective as a single treatment approach. (as is the case in TRT based approaches) effects seem modest at best. Treatment strategy might be best organized integrally, using a standardized approach in diagnostics, treatment and assessments because of the fact that using the approaches serially and at random might lead to unwanted increase of health utilization and costs. Moreover, a CBT based framework in tinnitus management is advisable.

PANEL 2. Usual Care Treatment protocol			
	Contact (min)	**Professional**	**Activities**
Step 1 (T0 – T1)	Audiological diagnostics (105)	Audiological assistant	Pure tone and speech audiometry, Tympanometry (stapedial reflexes) Tinnitus analyses: Pitch Mask Frequency and Minimum Masking Level Uncomfortable Loudness Level measurement Hearing aid check and optimisation (if present) Questions about duration and location of the tinnitus
		Clinical physicist in audiology (CPA)	Individual consult by clinical physicist in audiology Audiological anamnesis Assessment of audiometry and explanation Information about tinnitus and hearing loss Assessment severity of complaints When indicated: prescription hearing aid / prescription tinnitus masker*
	Audiological rehabilitation (30)	Audiology assistant	Check up after 8 weeks of hearing aid-usage Hearing aid check and optimisation
	Audiological Follow-up (40)	Audiology assistent	Pure tone and speech audiometry, Tympanometry (stapedial reflexes) Uncomfortable Loudness Level measurement Hearing aid check and optimisation (if present) Tinnitus analyses: Pitch Mask Frequency and Minimum Masking Level
		CPA	Individual consult by clinical physicist in audiology When indicated: Referral to social work
Step 2 (T1 – T2)	Intake Social work (60)	Social worker	General inventory of complaints and use of hearing aids/maskers When indicated: Social work trajectory of maximum 9 follow-up contacts
	Follow-up Social work (60)	Social worker	Maximum 9 contacts including Counseling sessions Telephone contacts Extraneous appointments with third parties House calls

Treatment fidelity

Treatment fidelity was assessed by a post-hoc investigation of CRF's, patient-attendance lists, and electronic databases, on a random sample of 40 cases per condition, in order to verify whether both UC and SC were performed according to treatment-protocols (adherence), and not overly influenced (contamination) by contrasting elements from the other treatment (Leeuw et al., 2009).

PANEL 3. Specialized Care Treatment protocol			
	Contact (min)	**Professional**	**Activities**
Step 1 (T0 – T1)	Audiological diagnostics (105)	Audiology assistant	Pure tone and speech audiometry, Tympanometry (stapedial reflexes) Tinnitus analyses: Pitch Mask Frequency and Minimum Masking Level Uncomfortable Loudness Level measurement Hearing aid check and optimisation (if present) Tinnitus anamnesis using structured interview
		Clinical physicist in audiology (CPA)	Individual consult by clinical physicist in audiology ** Audiological anamnesis, assessment of audiometry and explanation Information about tinnitus and hearing loss Introduction to the neurophysiological model (Jastreboff, 1990) Reading materials and treatment rationale are provided Explanation of treatment protocol in the first step and explanation of stepped-care approach When indicated: prescription hearing aid / prescription sound generator*
	Audiological rehabilitation (30)	Audiology assistant	Check up after 8 weeks of hearing aid/masking device -usage Hearing aid check /masking device and optimisation
	Tinnitus educational session (120)	Psychology assistant	The basics of the TRT are explained The NF model is explained extensively Fear-avoidance is discussed General information about second step care is provided Patients are enabled to have a group discussion and ask remaining questions
	Intake Psychology: (60)	Psychologist	When indicated by scores on TQ, THI and anamnesis; Treatment goals for step 2 are formulated in concordance with patient and the patient is planned in multidisciplinary team meeting
Step 2 (T1 – T2)	Audiological follow-up (40)	Audiology assistant	Pure tone and speech audiometry, Tympanometry (stapedial reflexes) Tinnitus analyses: Pitch Mask Frequency and Minimum Masking Level Uncomfortable Loudness Level measurement Hearing aid check and optimisation (if present)
		CPA (TRT)	Individual consult by clinical physicist in audiology **
	Multidisciplinary team meeting (10/patient)	All professionals involved in SC	All tinnitus patients are discussed and, when indicated by scores on TQ/THI and clinical view of psychologist, multidisciplinary treatment goals for step 2 are integrated in a plan of treatment
	Group treatments A, B, or C (120/session)	Psychologist Movement therapist Physical therapist	1. Group sessions: CBT; Psycho education, cognitive restructuring, exposure techniques, mindfulness-based elements, stress relieve & attention redirecting techniques by means of

Step 2 (T1 – T2)	Group treatments A, B, or C (120/session)	Psychologist Movement therapist Physical therapist CPA Social worker Speech-therapist	1. Group sessions: CBT; Psycho education, cognitive restructuring, exposure techniques, mindfulness-based elements, stress relieve & attention redirecting techniques by means of movement therapy, and applied relaxation (intensity varies across group-treatments A, B, and C) 2. Themed group counseling sessions (including partners)
	Individual Trajectory in case of contra indication for group treatment (60/per discipline)	Psychologist Movement therapist	Combination of the above mentioned group treatment principles applied on individual basis *(With optional addition of a combination of professionals involved in group treatments)*

* Sound-generators were prescribed when specifically asked for by the patient and were fitted by using a small band noise around the Pitch Match Frequency, presented slightly above hearing threshold, as measured with the small band noise of the sound generator.
** Specifically the counseling elements of TRT were part of intervention; educating patients about tinnitus and the neuro-physiological model

Outcomes

Stratification assessment

To assess hearing impairment, pure tone audiometry was performed bilaterally on 1, 2, and 4 kHz, using a mobile audiometer (Interacoustics AS208) with audiometry headphones (Telephonics TDH-39, Peltorcapped) and the PTA for 1, 2 and 4 kHz (stratification cut-off point at 60 dB hearing level in worst ear) was calculated. The Tinnitus Questionnaire was used to assess Tinnitus-severity at baseline (stratification cut-off point at a score of 47) (Rief et al., 2005).

Primary outcome measures

The HUI Mark III is a 17-item questionnaire to assess health-related quality of life or generic health on eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/complaints. Each question has five or six levels, and 972.000 possible health states can be computed. Possible utility scores range from -0.36 to 1.00 for the HUI Mark III (Feeny et al., 2002). The HUI has shown adequate responsiveness in the tinnitus population (Maes et al., 2011). Tinnitus-severity was assessed by the Tinnitus Questionnaire (TQ) (Hallam et al., 1988). The TQ consists of 52 items rated on a 3-point scale and assesses psychological distress associated with tinnitus. Psychometric properties of the TQ have proven excellent in different languages (Meeus et al., 2007). The Tinnitus Handicap Inventory (THI) is a 25 item instrument scored on a 3-label category scale. The THI assesses tinnitus-related impairment on 3 domains; functional, emotional and catastrophic (Bartels et al., 2008; Newman et al., 1996; Newman et al., 1998). Both overall and subscale internal consistency were found to be satisfactory in the current sample.

Secondary outcome measures

Negative affect was measured with the Hospital Anxiety and Depression Scale (HADS), which contains 14 items and has good reliability and validity (Spinhoven et al., 1997). The Tinnitus Catastrophizing Scale (TCS) is an adapted version of the Pain Catastrophizing Scale (Van Damme et al., 2002). The TCS assesses catastrophic mis-interpretations of the tinnitus

sound and has 13 items to be rated on a 5-point scale (0 = not at all, 4 = always). The TCS has been tested with patients (Cima, Crombez et al., 2011), and internal consistency of the total TCS score in the current sample was excellent (Cronbach's alpha = .94). The Fear of Tinnitus Questionnaire (FTQ) measures tinnitus-related fear. Some of the FTQ items were derived from the Tampa Scale for Kinesiophobia and the Pain Anxiety Symptoms Scale (McCracken et al., 1992; Roelofs et al., 2007). The FTQ was pre-tested with patients (Cima, Crombez et al., 2011), and has 17 items to be rated on a true or false scale. Internal consistency of the total FTQ score in the current sample was excellent as well (Cronbach's alpha = .82).
Demographic data were gathered by a 5-item questionnaire to establish gender, age, duration of complaints, educational level and adherence area.

Sample size
Only one study on quality of life of tinnitus patients receiving specialized tinnitus care was identified. The observed change of 0.065 in health state utility score in that study (El Refaie et al., 2004), with a standard deviation of 0.15, as measured with the Short Form-36 (Hays et al., 1993), was used to calculate our sample size. Given $\alpha = 0.05$ (2-sided) and power = 80%, and taking into account 15% loss to follow-up, this resulted in 99 patients per condition (total n = 198).
A post-calculation was performed mid-trial for detecting a relevant difference within the patient-subgroup receiving step-2 treatment. As our step-2 treatment is comparable with treatment in an earlier study, the effect size of $d = 0.62$ on the TQ in that study was used to compute power for our step-2 (Kroner-Herwig et al., 2003). Given $\alpha=0.05$ (two-sided) and power = 80%, n=41 patients per condition were needed in the 2nd step of care. Assuming that 21% of all patients entering step-1 would enter the step-2, and taking into account 15% attrition, n=232 patients were needed per condition in step-1 (total n = 464). The increment in inclusion was approved by the Medical Ethical Board (METC-SRL: 08/07/2008) and the steering committee of the funding party (ZonMW).

Statistical analysis

The Consolidated Standards of Reporting Trials (CONSORT) was employed to report results (Hopewell et al., 2008). All statistical analysis were performed with PASW SPSS statistical software version 18.0.(SPSS, 2009)

Protocol-adherence and contamination check
Protocol-adherence was assessed by dividing the number of required observed elements (essential and unique and essential but not unique), by the maximum possible number of these elements. Treatment contamination was assessed by dividing the number of observed not allowed treatment elements by the maximum number of these elements (Leeuw et al., 2009). To check for equality of adherence and contamination scores for both UC and SC over rated treatment charts an analysis of variance was carried out.

Treatment outcome: intention-to-treat analyses
Intention-to-treat analyses were employed; all patients who were measured at baseline and allocated to treatment were included, irrespective of their participation in subsequent treatment or follow-up measurements. Mixed (multilevel) regression analyses were carried out on all available data per outcome, without imputation of missing data, using treatment, time and covariates as predictors. Details of the mixed model are found in appendix A.

Moderation of tinnitus-severity
To check whether the difference between SC and UC treatment, as measured with the HUI (health-related quality of life) and the HADS (general negative affect), was different for patients suffering severely from the tinnitus (TQ) and entering step-2, than for those who were only mildly affected receiving step-1 care only, the interaction between tinnitus-severity at baseline and treatment was tested (α=.01 for the interaction test with respect to these outcome parameters).

Role of funding source
The funding party was not involved in study design, data collection, data analysis, data interpretation or the preparation of the report. Participation of RFFC, IM, MJ, LA and JWSV was supported by the ZonMw Grant, number: 945-07-715, and all had access to the data. All authors commented on drafts and approved the final report. RFFC had final responsibility for the decision to submit the paper for publication. There were no conflicts of interest.

Results

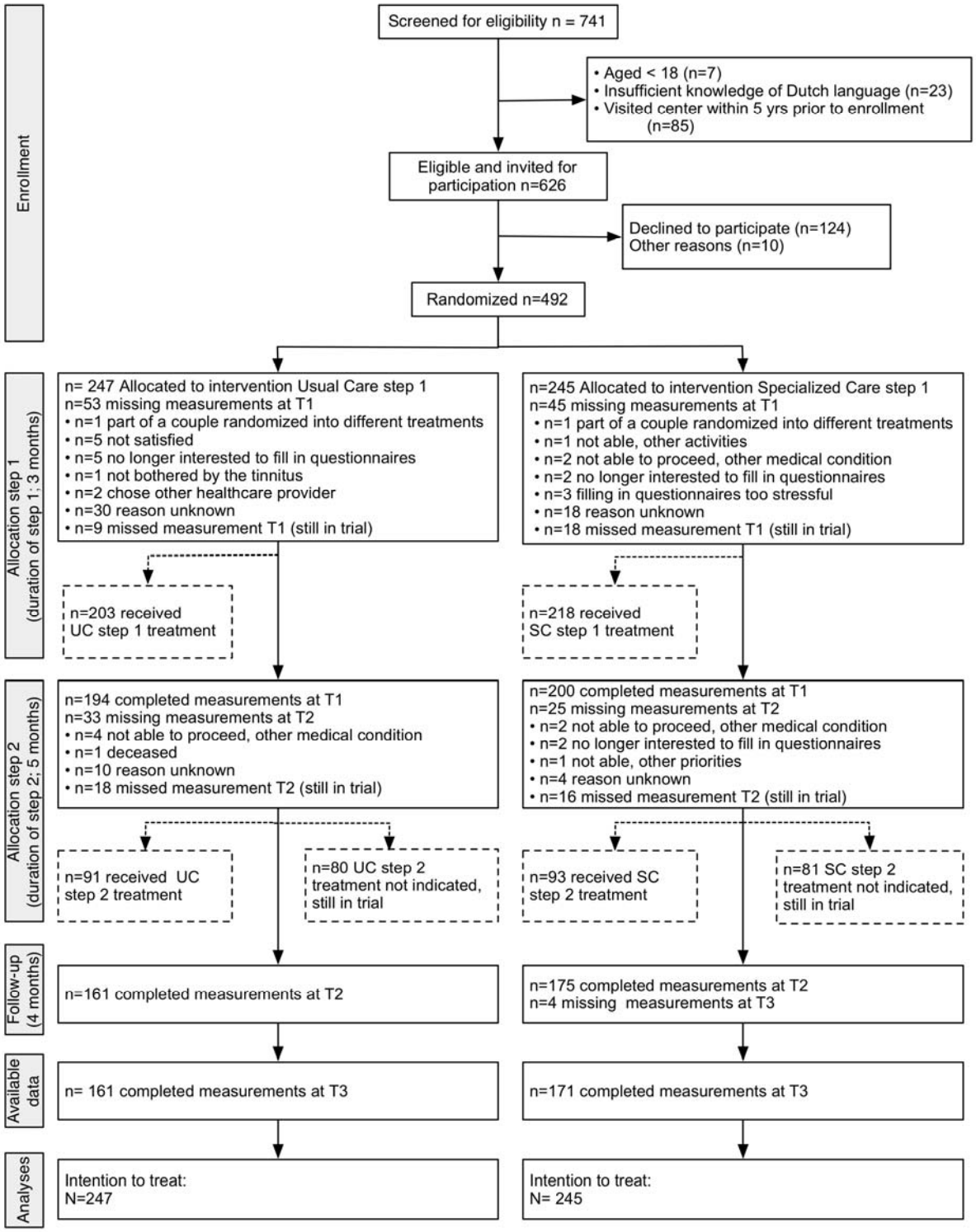
Flow of participants

Figure 2 shows the flow of participants, including drop-outs, non-responders, reasons for non-response for measurements at one of the follow-ups, and reasons for drop-out if known. Non-response was defined as: measurements were missed at one or more of the follow-ups, nonetheless participants remained in the trial; drop-out was defined as: participants left the trial permanently and told us so. Of the 741 participants screened for eligibility, 626 were invited for participation, and 492 completed baseline measurements and were randomized to step-1 treatment; of whom 247 were allocated to UC, and 245 to SC treatment. Randomization and allocation took place from September 2007 until December 2009. Follow-up measurements were completed in January 2011.
Non-response and drop-out rates per time point did not differ between groups (α=.01, $p>.20$), as measured with logistic regression, using missingness (whether due to non-response or dropout) as outcome (0=not missing, 1=missing), and group, baseline covariates (age, gender, education, duration of complaints, tinnitus-severity at baseline and hearing loss) and scores on the HUI, the TQ and the THI on the previous time-point as predictors. Only age was predictive for missingness, with increasing age giving more missingness ($p<.01$ for age at time points 1 and 2, $p>.083$ for all other predictors and time points). All baseline covariates were included into all outcome analyses.
From randomization to final follow-up, a loss to follow-up was observed of 34.8% and 30.2% in the UC and SC group respectively. The reasons for non-response seem not to be related to treatment content.
The baseline values for all variables, tinnitus characteristics, and audiological data for the total sample, and for UC and SC separately, are displayed in table 1.

Protocol-adherence and contamination check

Interrater-reliability between both raters for the identification of treatment-condition was excellent (Cohen's kappa = .96), and good for the identification of step-2 treatment and for specific treatments-elements (Cohen's kappa = .79 and .74 respectively). Analysis of variance indicated no significant differences between treatment-conditions in protocol-adherence and contamination ($P>.60$), using the mean scores of adherence and contamination over all rated CRF's.
In 97% of the cases correct classification of treatment-condition of the observed elements occurred (0=UC, 1=SC), supporting sufficient differentiation between treatment-conditions. On average 87.5% of essential treatment-elements (unique and not unique) occurred during

the delivery of both treatments (0='did not occur', 1='did occur') (Mean=88.4%, SD=9.02 for UC, and Mean=87.5%, SD=12.6 for SC), indicating satisfactory protocol-adherence. On average 6% (Mean=4.6% and SD=2.6 for UC, and Mean=8.1%, SD=6.1 for SC) of the prohibited treatment-elements occurred during treatment delivery, demonstrating absence of contamination.



UC= Usual Care; SC=Specialized Care, T0=Month 0, T1=Month 3, T2=Month 8, T3=Month 12

Figure 2. Flow of participants (CONSORT)

Table 1. Summary of demographic characteristics, baseline mean values on primary and secondary outcome measures, tinnitus characteristics, and audiometric data of the all participants, and for each group separately

	Total (n=492)	**UC (n=247)**	**SC (n=245)**
Age in yrs (SD)	54.19 (11.5)	54.63 (12.0)	53.74 (11.0)
Gender (% male)	62.6	60.7	64.6
Education (%)			
Low	45.7	47.3	44.0
Middle	27.7	24.5	30.9
High	26.6	28.2	25.1
Employment (% yes)	53.4	50.2	56.6
Duration (%)			
Less than 1 yr	29.9	32.7	27.2
1 to 5 yrs	38.9	37.9	39.9
More than 5 yrs	31.1	29.4	32.9
Mild complaints TQ<47 (%)	45.5	45.3	45.7
Tinnitus sound: pure tone (%)	14.5	9.9	17.8
Tinnitus left (ear/head) (%)	25.0	24.8	25.2
Tinnitus right (ear/head) (%)	19.9	19.6	20.1
Continuous tinnitus (%)	83.9	83.3	84.5
Interval tinnitus (%)	6.9	3.0	10.7
Fitting of hearing aid (% yes)	18.5	18.2	18.6
Fitting of sound generator (% yes)	18.9	18.6	19.2
PTA right ear (SD)	29.74 (19.4)	30.30 (20.6)	29.18 (18.2)
PTA left ear (SD)	31.05 (20.6)	30.96 (20.3)	31.14 (21.1)
PTA bilateral (SD)	30.57 (17.6)	30.77 (17.9)	30.37 (17.4)
TQ (SD)	49.05 (18.9)	48.78 (19.2)	49.32 (18.5)
TCS (SD)	21.11 (12.2)	21.36 (12.6)	20.86 (11.8)
FTQ (SD)	7.25 (3.6)	7.31 (3.7)	7.19 (3.5)
THI (SD)	38.96 (22.9)	38.65 (23.2)	39.27 (22.6)
HUI (SD)	0.635 (0.3)	0.641 (0.3)	0.629 (0.3)
HADS (SD)	12.20 (8.0)	11.79 (8.0)	12.60 (8.1)

UC=Usual Care, SC=Specialized Care, SD=standard deviation, PTA=Pure tone average for 1, 2 and 4 kHz, TQ=Tinnitus Questionnaire, TCS=Tinnitus Catastrophizing Scale, FTQ=Fear of Tinnitus Questionnaire, THI=Tinnitus Handicap Inventory, HUI=Health Utilities Index, HADS=Hospital Anxiety and Depression Scale

Treatment outcome: Intention-to-treat analyses

Significant group differences were found on all outcomes (See Table 2 and 3, and Figure 3). Group differences favouring SC in health-related quality of life (HUI) were significant at the second and third follow-up ($p<.05$ and $p<.01$ respectively). Differences in favour of SC with respect to tinnitus-severity (TQ) and tinnitus-related impairment (THI) were found on all 3 follow-ups ($p<.01$ at follow-up 1, and $p<.001$ at follow-up 2 and 3). Groups also differed, favouring SC, in negative affect (HADS) at the last two follow-ups ($p<.001$ at follow-up 2, and $p<.01$ at follow-up 3), and in tinnitus catastrophizing (TCS) and tinnitus-related fear (FTQ) on all three follow-ups ($p < .01$ at follow-up 1, $p < .001$ at follow-up 2 and 3). Results indicate that the difference between SC and UC was equal at follow-ups 2 and 3, and larger than at follow-up 1. This simplified treatment-effect pattern was tested against the general model as follows): the terms group*t1, group*t2, group*t3 were replaced with a single term

group*time, with time coded as 0,0,1,1 for the HUI and 0,1,2,2 for all other outcomes. For all six outcomes, the simplified treatment-effect pattern was supported (p>.05 for the Likelihood Ratio test with df=2), indicating that the outcome difference between SC and UC increased from baseline to month 8 and remained stable from month 8 to 12.

Table 2. Observed means and standard deviations (SD) based on all available data for the outcomes at baseline, T1 (after step 1, 3 months after baseline), T2 (after step 2, 8 months after baseline) and T3 (4 months follow-up, 12 months after baseline)

	Baseline	**T1**	**T2**	**T3**
	UC (n=247)	UC (n=194)	UC (n=161)	UC (n=161)
	SC (n=245)	SC (n=200)	SC (n=175)	SC (n=171)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Primary outcomes				
Health-related QoL (HUI)				
UC	0.641 (.30)	0.640 (.29)	0.634 (0.29)	0.631 (0.28)
SC	0.628 (.28)	0.620 (.29)	0.656 (0.25)	0.681 (0.25)
Tinnitus Severity (TQ)				
UC	48.87 (19.22)	45.51 (19.65)	42.36 (19.62)	42.12 (19.81)
SC	49.39 (18.50)	42.01 (19.81)	36.47 (17.48)	33.43 (16.89)
Tinnitus impairment (THI)				
UC	38.73 (23.20)	37.38 (23.74)	34.14 (24.60)	33.51 (23.25)
SC	39.25 (22.65)	34.25 (23.44)	28.85 (20.51)	26.45 (18.81)
Secondary outcomes				
Negative affect (HADS)				
UC	11.83.(8.03)	12.08 (8.75)	11.47 (8.55)	10.83 (8.03)
SC	12.61 (8.07)	11.91 (7.96)	10.52 (7.21)	10.22 (7.01)
Tinnitus catastrophising (TCS)				
UC	21.42 (12.56)	18.65 (11.76)	17.14 (11.54)	15.95 (11.79)
SC	20.89 (11.83)	16.20 (11.65)	12.45 (10.30)	11.73 (9.91)
Tinnitus related fear (FTQ)				
UC	7.32 (3.66)	6.60 (3.70)	6.19 (4.06)	6.04 (4.00)
SC	7.19 (3.54)	5.60 (3.87)	4.52 (3.50)	4.20 (3.16)

QoL=Quality of life, UC=Usual Care, SC=Specialized Care, SD=Standard deviation, HUI=Health Utilities index, TQ=Tinnitus Questionnaire, THI=Tinnitus Handicap Inventory, HADS=Hospital Anxiety and Depression Scale, TCS=Tinnitus Catastrophizing Scale, FTQ=Fear of Tinnitus Questionnaire

Moderation of Tinnitus-severity on treatment effect

No significant interaction effect of tinnitus-severity and treatment on the HUI or the HADS was found at any of the time-points (df=3, p=.26 and df=3, p=.33 respectively), indicating that the difference between treatment-groups as measured with the HUI or the HADS did not depend on the level of tinnitus-severity as measured with the TQ.

Table 3. Estimated Group difference (B) and 95% confidence intervals (C.I.) on primary and secondary outcomes at follow-up 1 (3 months), follow-up 2 (8 months), and follow-up 3 (12 months), based on intention to treat analysis

Primary outcomes	**B**	**95% C.I.**		**P**	**E.S.**
Health-related QoL (HUI)[a]					
3 months	-0.01	0.06	0.04	.642	0.04
8 months	0.04	0.01	0.07	.026	0.18
12 months	0.06	0.03	0.09	.001	0.24
Tinnitus Severity (TQ)[b]					
3 months	-3.31	-5.61	-1.02	.005	0.20
8 months	-7.07	-9.56	-4.58	.000	0.41
12 months	-8.06	-10.83	-5.30	.000	0.43
Tinnitus impairment (THI)[c]					
3 months	-4.26	-7.07	-1.45	.003	0.32
8 months	-7.63	-10.71	-4.54	.000	0.52
12 months	-7.51	-10.66	-4.35	.000	0.45
Secondary outcomes	**B**	**99% C.I.**		**P**	**E.S.**
Negative affect (HADS)[d]					
3 months	-0.86	-2.18	0.47	.094	0.15
8 months	-2.09	-3.51	-0.66	.000	0.35
12 months	-1.51	-2.87	-0.15	.004	0.24
Tinnitus catastrophising (TCS)[e]					
3 months	-2.10	-3.96	-0.25	.004	0.31
8 months	-4.68	-6.94	-2.43	.000	0.60
12 months	-3.83	-6.19	-1.48	.000	0.41
Tinnitus related fear (FTQ)[f]					
3 months	-0.79	-1.49	-0.08	.004	0.35
8 months	-1.55	-2.35	-0.75	.000	0.58
12 months	-1.50	-2.32	-0.69	.000	0.48

QoL=Quality of life, SD=Standard deviation, HUI=Health Utilities Index, TQ=Tinnitus Questionnaire, THI=Tinnitus HandicapInventory, HADS=Hospital Anxiety and Depression Scale, TCS=Tinnitus Catastrophizing Scale, FTQ=Fear of Tinnitus Questionnaire, UC=Usual Care, SC=Specialized Care.
[1]Since UC is coded as 0 and SC as 1, a negative B shows lower scores in UC than SC at the follow-up measurements. The B's displayed are the group*time effects as shown in appendix B, where time=0 for baseline· time=1 for follow-up 1, time=2 for follow-up 2, and time=3 for follow-up 3
[2] E.S.=Effect size (absolute values), calculated by dividing the B's (ignoring their sign) by the square root of the average of residual variances at follow-up 1, 2 and 3, giving a mixed regression version of Cohen's d.
[a]Adjusted for the main effects of both stratifiers (hearing loss and tinnitus severity at baseline), and of time (using dummy coding with baseline as reference category); [b] Adjusted for the main effects of education, hearing loss, and time ; [c]Adjusted for the main effects of age, duration, education, tinnitus severity at baseline and time, and for interaction effects of time by education and by tinnitus severity at baseline; [d]Adjusted for the main effects of duration, both stratifiers, time, and for interaction effects of time by duration and by tinnitus severity at baseline; [e] Adjusted for the main effects of education, tinnitus severity at baseline, time, and for the interaction effects of time by education and by tinnitus severity at baseline; [f]Adjusted for the main effects tinnitus severity at baseline, time, ,and for the interaction effects of time by tinnitus severity at baseline

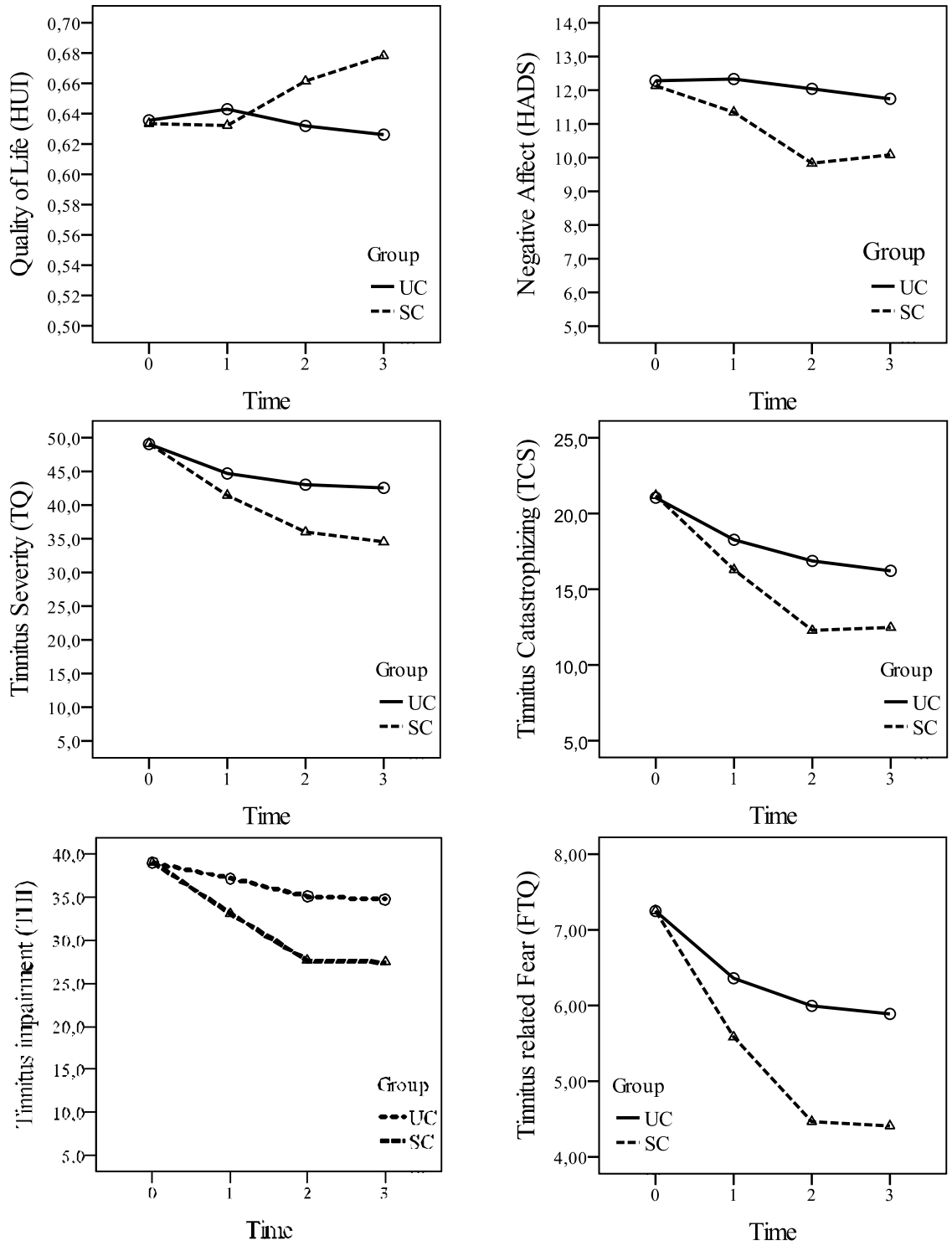


Figure 3. Graphs depicting changes over time in primary and secondary outcomes for both Usual Care (UC) and Specialized Care (SC); using predicting values from the final general models

Discussion

This study demonstrates that stepped-care tinnitus management, combining elements of TRT within a CBT-framework (SC), is more effective than usual care (UC) in increasing health-related quality of life, and reducing tinnitus-severity and tinnitus impairment. Additionally, SC compared to UC generates greater improvements in general negative emotional states, level of tinnitus-related catastrophic thinking and tinnitus-related fear. The effectiveness of SC as compared to UC has been demonstrated not only after the first 3 months of step-1 treatment, but also after the more intensive step-2 treatment approach, as well as after 4 months of no-treatment. Results are even more striking in that patients with mild tinnitus complaints, receiving step-1 treatment only, were included in all analyses. Furthermore, mild and severe tinnitus sufferers, as measured with the Tinnitus Questionnaire at baseline, appeared to benefit equally from getting SC treatment instead of UC treatment. These findings support our main hypothesis that a CBT based stepped care approach with elements from TRT, is effective in tinnitus management, both for milder forms of tinnitus suffering as well as for more severe tinnitus incapacitation.

Two main treatment-approaches have dominated the management of patients with tinnitus complaints. The TRT approach, with a focus on sound habituation, as well as the CBT approach, with a focus on dysfunctional beliefs about tinnitus and associated safety behaviors, have been widely applied and studied (Hesser et al., 2011; Hoare et al., 2010; Martinez-Devesa et al., 2010; Phillips & McFerran, 2010). However, a combination of the two, though previously proposed (Cima, et al., 2011; Seydel et al., 2010), has never before been investigated in a randomized controlled trial of this scale.

Particular strengths of our study are a relatively large sample size, the blinding of assessors, the assessment of treatment fidelity strengthening internal validity, and the delivery of the treatments according to protocols. Other strengths are the zero dropouts from step-2 treatment, the fact that both generic and tinnitus-specific outcome measures reveal consistent findings, and moreover, the differences between UC and SC treatment over time are likely to be clinically relevant. The percentage of patients reporting clinically relevant changes (Rief et al., 2005; Samsa et al., 1999) after 12 months in health-related quality of life and in tinnitus-severity was larger in the SC group.

There are also some limitations. First, our specialized care treatment consisted of several elements, and it is unclear which of those contributed to the overall effectiveness. Future studies might adopt a dismantling approach, leaving out potentially redundant treatment components in subsequent trials. Second, the treatment was carried out in an outpatient clinic for audiological rehabilitation. The question remains whether our results can be generalized to other healthcare settings, where generalizability is dependent on their similarity to the present setting. We are currently investigating implementation routes in both primary and secondary care.

Next to the analyses reported presently, first, moderation and mediation analyses are being carried out, providing additional information about underlying mechanisms of change, contributing to further refinement, tailoring, and increased effectiveness of the treatment. Second, cost-effectiveness data of SC compared to UC are not included currently, but are planned to be reported separately. Third, data was gathered using a seventh measure, the Tinnitus Coping and Cognitions List (TCCL). The main reason for including this measure was to test the psychometric properties of this new measure in patients with tinnitus. The TCCL has considerable content overlap with the TCS, therefore by omitting the TCCL from effect-analyses, crucial information is not missed currently and psychometric analysis is planned to be reported separately.

In conclusion, our findings provide firm evidence for an effective new treatment-approach in tinnitus-management. Results are highly relevant for clinical practice, given that best-practice

for tinnitus has not been defined yet (Hoare et al., 2010), leading to fragmentized costly treatment-trajectories (Cima et al., 2009). Delay of psycho-education and effective treatment is expected to aggravate tinnitus-complaints, increasing psychological strain and unnecessary prolongation of suffering. Current findings could lead to consensus in policy about best-practice in tinnitus-treatment, standard choices in referral-trajectories and the implementation of standardized tinnitus assessment and thereby comparable outcomes.

Acknowledgements

The authors would like to thank all professionals, supporting staff and management of Adelante; Audiology & Communication for enabling the RCT and to all participating tinnitus-patients. Special thanks are due to Marieke Jansen, Pauline Cox, and Martijn van Veghel for randomization, organization of off centre contacts, data entrance, and data management. We also express our appreciation to Rosanne Janssen for assisting with the online application 'Emium', Nele Vandebroek and Ken Ceulemans for their assistance in the treatment fidelity check, and the university hospital of Maastricht and Maastricht University, Faculty of Psychology and Neuroscience, for all supporting services.

Appendix A.

The mixed model for testing treatment effects on outcomes

Due to the randomization, pre-stratified on hearing loss and tinnitus severity, no significant baseline differences were expected between treatment conditions. However age, gender, education, hearing loss and tinnitus severity were included as covariates as to improve power. Since duration of complaints was a potentially relevant prognostic variable, this was added to the model as well[a]. The repeated measures per outcome were checked for multivariate outliers (mahalanobis distance, $p < .001$), and no such outliers were found for any outcome. Collinearity between covariates was checked but not found either, as all covariates had a variance inflation factor (VIF) below 1.5.

Since there were 4 repeated measures, time was entered in the mixed regression as a categorical variable using dummy coding[b], with the baseline as a reference category and a dummy indicator for every other time point (giving three dummies), to assess group differences in change from baseline, allowing for possible nonlinear change. To correct for multiple testing $\alpha=.05$ and $\alpha=.01$ (two-tailed) were used for primary and secondary outcomes, respectively.

The initial model included group, time, covariates, group by time, and covariate by time effects[c]. Each model change was tested for significance using Maximum Likelihood (ML) estimation and a likelihood ratio test with 'k' degrees of freedom (k=the difference in number of parameters between two successive models).

To enhance parsimony and increase interpretability of the model the following modelling steps were taken. First, every non-significant covariate by time interaction was removed, treating terms concerning the same predictor as one block with *d.f.*=3 (e.g. *cov*followup1*, *cov*followup2*, and *cov*followup3* in the panel below). Second, covariates that were neither significant nor involved in a *cov*time* term, were stepwise removed with *d.f.*=1, again using the same restrictive α's. Third, the 'main' group effect (β_1 in the equation) was dropped from the model, which is a valid and power-improving step in randomized trials.

Since baseline is the reference point, the 'main 'effect of 'group' actually reflects the group difference at baseline (see panel below). This effect is zero apart from sampling error due to randomization. The final mixed model per outcome was re-run with the restricted maximum likelihood method (REML) instead of ML to obtain better estimates of the standard errors.

[1] Categorical covariates were entered in the model using dummy coding, for Gender: 0 = male, 1 = female; Education dummy 1: 0 = low, 1 = middle, 0 = high; education dummy 2: 0 = low, 0 = middle, 1 = high. Each quantitative covariate was centred (Cov – sample mean = CovCen) and its quadratic form (CovCen * CovCen = CovCen2) was added to the model to assess possible nonlinear effects of the covariates on the outcomes.

[b] For each time point except baseline (the reference category) a dummy indicator was entered in the model.

[c] Prior to the initial models we tested each covariate by treatment interaction over time with a separate mixed regression model per covariate, with three way interactions of group, covariate and time and all corresponding lower order terms. No such three way interactions were found.

The mixed model equation for testing treatment effects on outcomes

$$y_{ti} = \beta_0 + \beta_{1\ group} + \beta_{2\ cov} + \beta_{3\ followup1} + \beta_{4\ followup2} + \beta_{5\ followup3} + \beta_{6\ group\ x\ followup1} + \beta_{7\ group\ x\ followup2} + \beta_{8\ group\ x\ followup3} + \beta_{9\ cov\ x\ followup1} + \beta_{10\ cov\ x\ followup2} + \beta_{11\ cov\ x\ followup3} + e_{ti}$$

Where:

t	=	Time
i	=	Patient identifier
group	=	0 for patients assigned to UC and 1 for patients assigned to SC
cov	=	The covariates: hearing level and tinnitus severity at baseline, age, gender, education, duration of complaints (see table 4) (the actual model contained multiple

covariates and covariate by time effects)

followup1 = 1 if t = 1 and 0 if else (see footnote 2 in section statistical analysis, treatment outcome), and likewise for followup2 (=1 if t=2 and 0 else) and followup 3 (= 1 if t=3 and 0 else)

e_{ti} = The random effect of patient *i* at time point *t*

With the following interpretation:

β_0 = The mean baseline in group 0 (UC)

β_1 = The mean baseline difference between groups (SC-UC) , expected to be zero due to the randomization

β_2 = The association between the specific covariate and the outcome at baseline

β_3 = The mean change from baseline to follow-up 1 (3 months after baseline) within patients who score 0 on all predictors included in the final model (e.g. group = UC, Gender = male, mean score on covariates), and likewise for β_4 (change from baseline to follow-up 2) and β_5 (change from baseline to follow-up 3)

β_6 = The group difference (SC-UC) in mean change from baseline to follow-up 1 (3 months after baseline), which is also the group difference at follow-up 1 since there is no difference at baseline, and likewise for β_7 (group difference in change from baseline to follow-up 2) and β_8 (group difference in change from baseline to follow-up 3)

β_9 = The effect of a specific covariate on the change from baseline to follow-up 1 in both treatment conditions, and likewise for β_{10} (covariate effect on change from baseline to follow-up 2) and β_{11} (covariate effect on change from baseline to follow-up 3)

The covariate * time interactions were dropped from the model if not significant, as assessed by a likelihood ratio test.
The null hypothesis of no difference between UC and SC implies that $\beta_6=\beta_7=\beta_8= 0$. This null hypothesis was tested against the alternative of a difference between treatments at follow-up 1, 2, and 3, with a likelihood test, df = 3
The null hypothesis of no difference between UC and SC at time point 1, follow-up 1, and an equal difference at time points 2 and 3, follow-up 2, and follow-up 3, implies that $\beta_6=0$; and $\beta_7 = \beta_8 \neq 0$. This hypothesis was tested against the general model, with a likelihood ratio test, df = 2
The null hypothesis of linear increase in difference at the first 2 time points, follow-up 1, and follow-up 2, and an equal difference at follow-up 3, implies that $2\beta_6 = \beta_7 = \beta_8 \neq 0$. This hypothesis was tested against the general model, with a likelihood ratio test, df = 2. The 4 random effects ($e_{1i,}$ $e_{2i,}$ $e_{3i,}$ e_{4i}) were assumed to be multivariate normally distributed with an unspecified covariance matrix, which is the most general covariance structure.

Appendix B.

Data collection for treatment effect

Baseline measurements were completed at the off-centre site, where respondents were assisted by one of four research assistants in using an internet-based environment. Two weeks prior to follow-up 1 (3 months after baseline), follow-up 2 (8 months after baseline), and follow-up 3 (12 months after baseline), personal log-in codes were sent by postal mail to every participant, enabling test completion online. If participants were not able to use the online system, either a paper version was sent to them by postal mail, or they were invited to the centre to receive help from a research assistant.

Data collection for treatment fidelity check

A trial specific measure was developed (Leeuw et al., 2009) enabling 2 independent assessors to rate whether specific treatment elements took place or not, without revealing whether or not these were required, allowed or prohibited and to assess the rater's judgement which treatment condition the treatment elements belonged to, and if Step-2 treatment was delivered. First, specific treatment elements were listed by two experts of both treatment protocols. Second, these experts categorized these elements into 5 categories; 1) Essential and unique, 2) Essential but not unique, 3) Unique but not essential, 4) Compatible, and 5) Prohibited. The content validity of this measure was supported by sufficient independent agreement (kappa=.83) between the two experts I categorizing all identified elements. Independent raters, both postgraduates in psychology, not involved in treatment, and not affiliated with the centre, rated a random sample of 40 CRF's per treatment condition and cross-checked occurrence of elements, using this measure. Imperative before treatment fidelity analysis were the following criteria. First, sufficient interrater reliability of the trial specific fidelity check instrument had to be established between the two independent raters (Cohen's Kappa>.70). Second, sufficient protocol adherence requires at least 70% of essential treatment elements have actually occurred (essential and unique, and essential but not unique). Third, contamination can be considered ignorable when no more than 10% of prohibited treatment elements occur.

CHAPTER 4

Cost-effectiveness of specialized treatment based on cognitive behavioral therapy versus usual care for tinnitus

Iris H.L. Maes, Rilana F.F. Cima, Lucien J.C. Anteunis, Dyon J.W.M. Scheyen, David M. Baguley, Amr El Refaie, Johannes W. Vlaeyen, Manuela A. Joore

Accepted for publication in Otology and Neurotology

Abstract

Objective Up to 21% of adults will develop tinnitus, manifesting the perception of a noxious disabling internal sound. Many different treatments are offered, but evidence on their effectiveness and cost-effectiveness is scarce or absent. Recently, the effectiveness of a specialized treatment of tinnitus based on cognitive behavioral therapy was demonstrated. The present study evaluates the cost-effectiveness of this treatment compared to care as usual, in an audiological centre.

Methods An economic evaluation was carried out alongside a randomized controlled clinical trial. The economic evaluation was conducted from a societal perspective, using a one-year time horizon. The incremental cost effectiveness ratio (ICER) was calculated by dividing the difference in costs by the difference in quality-adjusted life years (QALYs) based on the HUI Mark III. Non-parametric bootstrapping and sensitivity analyses were used to asses uncertainty in costs and effects. Sensitivity analysis included a complete cases analysis and analysis on data were missing values on the HUI Mark III were imputed based on a mixed regression model from the clinical effectiveness analysis.

Results Compared to patients receiving usual care, patients who received specialized care gained on average 0.015 QALYs (BCI:-0.028-0.055). The incremental costs from a societal perspective are $357 (95% BCI:-$1,034-$1,785). The incremental cost per QALY from a societal perspective amounted to $24,580. The probability that SC is cost-effective from a societal perspective is 58% for a willingness-to-pay for a QALY of $45,000.

Conclusion Specialized multidisciplinary tinnitus based on cognitive behavioral therapy may be cost-effective as compared to usual care.

Introduction

Tinnitus is the perception of a pernicious, and for some disabling sound for which there is no acoustic source. The prevalence of tinnitus in the western world is between 10-20% (Andersson, 2002; Davis & El Refaie, 2000) and approximately 3-5% of the general population is severely impaired by the tinnitus (Davis & El Refaie, 2000; Vesterager, 1997). There are several theories on the potential mechanisms that underlie tinnitus but none of these have been demonstrated scientifically (Henry et al., 2005). As a result there is no known drug or curative therapy at present (Ahmad & Seidman, 2004; Andersson et al., 2005) and tinnitus care is often fragmentized and costly (Lockwood et al., 2002). Tinnitus is known to cause affective problems, sleep difficulties and major impact upon concentration (Bartels et al., 2008; Davis & El Refaie, 2000; Henry et al., 2005). The combination of these complaints makes tinnitus sufferers feel exhausted and frustrated, resulting in diminished quality of life for the sufferers and sometimes their extended family (El Refaie et al., 2004; Erlandsson & Hallberg, 2000; Jastreboff et al., 1996; Kroner-Herwig et al., 2003; Scott et al., 1990). Therefore, almost all therapies are focused on alleviating tinnitus related distress and improving quality of life (Henry et al., 2005). The most frequent used approaches in relieving tinnitus distress and improving quality of life involve counseling, and hearing aid fitting to compensate hearing loss or provide sound generators or tinnitus maskers, but there is mixed evidence to support their clinical effectiveness (Hoare et al., 2010; Hobson et al., 2010). Evidence regarding the efficacy of clinical interventions remains sparse, but there are indications of benefit from Tinnitus Retraining Therapy (Forti et al., 2009; Henry et al., 2007; Henry et al., 2002; Herraiz et al., 2007; Phillips & McFerran, 2010), Cognitive Behavioral Therapy (El Refaie et al., 2004; Gudex et al., 2009; Hesser et al., 2011; Martinez Devesa et al., 2007) and a combination of therapies (Hoare et al., 2010). Tinnitus Retraining Therapy (TRT) is based on the neurophysiologic model of tinnitus developed by Jastreboff (Jastreboff et al., 1996). TRT involves [1] extensive directive counseling about tinnitus to reduce aversive reactions to the symptom and [2] sound therapy to facilitate habituation to the tinnitus signal (Jastreboff et al., 1996). Cognitive behavioral therapy is used to alter psychological processes that are considered to maintain or contribute to tinnitus-related complaints. Treatments that combine counseling and a listening device are also effective (El Refaie et al., 2004; Gudex et al., 2009). A study by El Refaie et al. (El Refaie et al., 2004) even found a significant effect on the SF-6D health state utilities. In the recent literature an integrated approach to treatment that combines insights from audiology, otology, psychology and other disciplines is promoted (Andersson et al., 2005). Recently, the first convincing results were demonstrated that such a multidisciplinary approach is effective in the treatment of tinnitus (R. F. Cima et al., 2012; Langguth, 2012). Patients improved in health-related quality of life, tinnitus severity and disability due to tinnitus. However, several regulatory authorities also emphasize the impact of assessing the value in healthcare programs (NICE, 2008; RVZ, 2006), to assess whether health is improved at a reasonable price. This is critically important in a condition like tinnitus since it is known to be costly to people who have it and to society at large (Maes et al., 2013). To our knowledge this is the first study of a multidisciplinary tinnitus treatment that involves a complete health economic evaluation. The objective of this study was to determine the cost-effectiveness of a specialized multidisciplinary tinnitus treatment based on cognitive behavioral therapy, compared to care as usual, in an audiological centre.

Methods

Study Design

An economic evaluation was performed alongside a randomized controlled clinical trial in an audiological centre in the Netherlands (Adelante Audiology and Communication, location

Hoensbroek). Patients were allocated to specialized multidisciplinary treatment based on cognitive behavioral therapy, which will be referred to as Specialized Care (SC), or Usual Care (UC), both provided by the audiological centre. Measures were taken for blinding patients to treatment assignment. Follow-up took place at three, eight and twelve months after randomization, with a no-contact period in the last 4 months in the trial. Non responders were monitored and at follow-up measurements contacted by telephone and reminded about the follow-up, up to two weeks after expiry of the due date. For assessing the cost-effectiveness, the SC group was compared to the UC group. The analyses were performed from a societal perspective, meaning that healthcare costs, patient & family costs and productivity losses are included.

Interventions

SC was based on a stepped-care approach, tailored to individual patient needs. The first step of SC consists of a multidisciplinary intervention for all patients, including audiological diagnostics and intervention (counseling, prescription of hearing aid and/or sound generator), a Tinnitus Educational Group session and an individual consult with a psychologist. Based on the scores of the TQ patients were classified into three different severity classes: mild ($TQ \leq 30$), moderate ($30 < TQ < 47$) or severe ($TQ \geq 47$) complaints and severe tinnitus complaints. For patients with mild complaints this basic intervention was expected to be sufficient. For patients with moderate to severe complaints a second step was offered that consists of two main group programs. Program A for patients suffering from tinnitus on a moderate to severe level consisted of 12 weekly group session. Program B for patients with severe tinnitus complaints consisted of 24 bi-weekly group sessions. Both programs comprise key elements of cognitive-behavioral therapy, education, relaxation techniques, attention diversion, exposure in daily life situations, and tinnitus retraining therapy.

UC consisted of a standardized version of the treatment that is currently applied in audiological centers throughout the Netherlands for tinnitus patients. UC was organized in a stepped care manner and consisted in step 1 of audiological diagnostics and intervention (counseling, prescription of hearing aid and/or sound generator) and, in step 2 if necessary, one or more consultations with a social worker with a maximum of ten one-hour-sessions (See Cima et al., 2009) for more detailed information).

Participants

The study population consisted of tinnitus sufferers referred to the audiological centre, with subjective tinnitus complaints, aged 18 years and older. Patients were excluded from the study if they were not able to read and write in Dutch. Patients who declared in writing to be willing to participate were invited for a first off-centre assessment contact, after which they were allocated to either to UC or SC.

Effects

The primary effect parameter in the economic evaluation is the quality-adjusted life year (QALY). The QALY is based on health state utilities measured with the Health Utilities Index Mark III (HUI). The HUI is a 17 item questionnaire to assess generic health-related quality of life on eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/complaints. Patients with tinnitus especially have complaints in the pain, cognition, emotion and hearing dimension (Maes et al., 2011). A multiplicative utility scoring function was used to determine the utility scores which range from -0.36 to 1.00 (Feeny et al., 2002). The minimal clinically relevant difference in these utility scores is considered to be 0.03 points (Horsman et al., 2003; Marra et al., 2005). The HUI has shown adequate

responsiveness in a tinnitus population (Maes et al., 2011). The utility scores were used to calculate QALYs using the area under the curve midpoint method (Drummond et al., 2005):
$QALY_i = ((U_{i,t0} + U_{i,t1})/2) * T_1(t_1 - t_0) + ((U_{i,t1} + U_{i,t2})/2) * T_2(t_2 - t_1) + ((U_{i,t2} + U_{i,t3})/2) * T_3(t_3 - t_2)$

Cost Analysis

Costs[1] in the analysis include healthcare costs, patient and family costs, and indirect costs. The healthcare costs consisted of the costs of tinnitus care as provided at the audiological centre, and other healthcare costs associated with tinnitus. The exact amount of care consumed at the audiological centre by each patient was registered in clinical record forms. The unit costs of a hearing aid were taken from the GIP databank[2] 2009, and the costs of hearing aid fitting were based on information from the Dutch Association of Hearing Aid Dispensers. The unit cost of a tinnitus masking device was determined based on personal communication with several hearing aid dispensers. The unit costs of Treatment Group A and B, Individual Treatment and the Tinnitus Educational Group session in SC were determined by a cost calculation. This cost calculation was based on a registration of personnel time and materials used, after which overhead was included. Salary costs for each discipline were based on the average salary per scale (employer's costs included) that are normally used in Dutch audiological centers in 2009. Unit costs of material were market prices from 2009. The depreciation period of the variable material costs was 5 years. The rental of the gym was based on the invoice from the audiological centre of 2009. As recommended (Hakkaart - van Roijen et al., 2010) an overhead of 35.5% was calculated over the total costs. Prices of individual treatment were calculated based on the number of contacts the patient had with each healthcare professional. The costs of the Tinnitus Educational Group session were calculated by multiplying the average hourly salary scale of an audiological assistant ($36.89) by 240 minutes (including 120 minutes of group session and 10 minutes indirect time per patient). Total costs of the Tinnitus Educational Group session were $197.01 (including 35.5% overhead costs). Since 12 patients can participate in this group the unit cost per patient is $16.42. All remaining unit costs of tinnitus care at the audiological centre were based on an anonymous source.[3]

Other healthcare costs associated with tinnitus included contacts with the general practitioner practice, hospital care, care provided by other healthcare professionals, and medication. This resource use was measured using a self-administered cost questionnaire with a recall period of three months. The questionnaire was administered at each follow-up measurement. The unit costs of the other healthcare costs were adopted from the Dutch guideline for cost research (Hakkaart - van Roijen et al., 2010) unless stated otherwise (Table 3). The cost questionnaire included items to measure patient and family costs in the three months prior to the follow-up measurement (travel expenses, over the counter medication and other expenses). In the final analysis these costs were interpolated to yearly costs by using the following formula (Drummond et al., 2005): $Cost_i = C_{i,t1} + (C_{i,t2}/3) * 5 + (C_{i,t3})/3) * 4$.

Also included in the cost questionnaire were the PRODISQ items (Koopmanschap, 2005) to measure loss of productivity (indirect costs). The costs of loss of productivity were quantified using the friction cost method, as recommended in the Netherlands (Hakkaart - van Roijen et al., 2010). Whenever necessary, unit costs were converted to the reference year 2009 by means of price index figures.

[1] All costs were converted to U.S. dollars according to the following exchange rate (1 euro = $ 1.25)

[2] The GIP databank is an information system of the Health Care Insurance containing information on expenditure on (extramural) drugs and medical aids under the Health Care insurance act.

[3] In the current Dutch health care system organizations negotiate unit costs of (some of) their products with health care insurance companies. Therefore, some unit costs are business confidential. As a result, it was decided not to reveal the source of unit costs for these care components.

Statistical analysis

Baseline data on utilities and costs were tested for normality with a Kolmogorov-Smirnov test. Differences between the groups on baseline utility scores and costs were compared with an independent samples t-test or a Mann-Whitney U test, depending on the test for normality. Analyses were performed from both the societal and the healthcare perspective. First, mean incremental (societal or healthcare) costs and QALYs per patient between SC and UC were calculated. Incremental cost-utility ratios were calculated by dividing the mean incremental (societal or healthcare) costs per patient by the mean incremental QALY per patient. In the Netherlands there is no formal threshold for cost-effectiveness therefore a maximum willingness-to-pay per QALY of £30.000 (approximately $45.000) was used in accordance with the NICE guidelines (Devlin & Parkin, 2004; Raftery, 2001). Incomplete data (missing items) on the HUI Mark III were imputed using missing value analysis based on regression in SPSS version 18. Complete missing data on HUI Mark III and missing data on the cost questionnaires were calculated using Rubin's multiple imputation (Rubin, 1987) in SPSS version 18. This method generates 5 different data sets for imputed data. All analyses were performed with each of these 5 data sets and these results were pooled. Uncertainty in the incremental costs, outcomes and cost-effectiveness was evaluated using non-parametric bootstrapping with 1,000 simulations in Excel. In a non-parametric bootstrap simulation cost and effectiveness pairs are randomly drawn, with replacement, from the data to obtain a sample equal the original sample size. In order to get 1,000 estimates of the incremental costs and effect, this procedure is repeated 1,000 times. Bootstrapped confidence intervals for the (incremental) costs and QALYs were determined by taking the 2.5th and 97.5th percentile. Uncertainty of the incremental cost-effectiveness ratio is shown in cost-effectiveness planes. The probability that specialized tinnitus care provided in a specialized tinnitus centre is more cost-effective than usual care, depends on what society is willing to pay per unit of gain in effectiveness, the so-called willingness-to-pay threshold. The net monetary benefit for different thresholds was calculated by subtracting the incremental costs from the incremental effects, multiplied by the ceiling ratio. Cost-effectiveness acceptability curves show the probability that an intervention has the highest net monetary benefit, and is thus considered cost-effective, given different willingness-to-pay thresholds for a QALY.

Sensitivity analyses

As recommended by Blough et al. (Blough et al., 2009), sensitivity analyses were used to show the impact of different ways of handling missing values. In the clinical effectiveness analysis of this trial (Cima et al., 2012) a series of mixed (multilevel) regression analyses were carried out, in which all available data are used without the need for imputation of missing data (Snijders & Bosker, 1999). In one of these analyses, the HUI utility score was used as dependent variable in a repeated measures design with group (US, SC) as the between-subject factor and time (baseline, follow-up 1, follow-up 2 and follow-up 3) as the within-subject factor. Predicted values were calculated from the regression equation of the final model. Since these models did not include cost data there was a small difference between these predicted values and the HUI utility scores calculated using multiple imputation. In the first sensitivity analysis the predicted values were used to impute missing values on the HUI utility scores. The second sensitivity analysis was a complete cases analysis, based on participants for whom both a QALY as well as total societal costs were available.

Results

Participants

Figure 1 shows the flow of participants, including drop-outs, non-responders, as well as reasons for non-response at one of the follow-up, or drop-out if known. Randomization and allocation started in September 2007 and ended in December 2009. Follow-up measurements were completed in January 2011. Of the 741 participants who were screened for eligibility, 626 were invited for participation and 492 were randomized to one of the treatment arms. 247 were randomized to UC and 245 to SC. Of the 203 participants that finished the first step of treatment in the UC, a total of 91 patients (46,9%) were identified as having more severe tinnitus complaints and received step 2 UC treatment. Of the 218 patients that finished the first step in SC, a total of 93 patients (46,7%) met criteria for step 2 treatment (TQ score > 47) and were treated. All patients diagnosed as having mild complaints, either in UC (41, 2%) or in SC (40, 7%), remained in the trial for follow-up measurements without treatment in the second step. Drop-out and non response rates per time point, and number of patients did not differ between groups (α=.01). From randomization to final follow-up, a loss to follow-up as a result of measurement attrition of 35% in the UC group and in the SC group of 30% was observed. The proportion of missing data and or non-response is acceptable for current analyses. The reasons for non-response seem not to be related to treatment content.

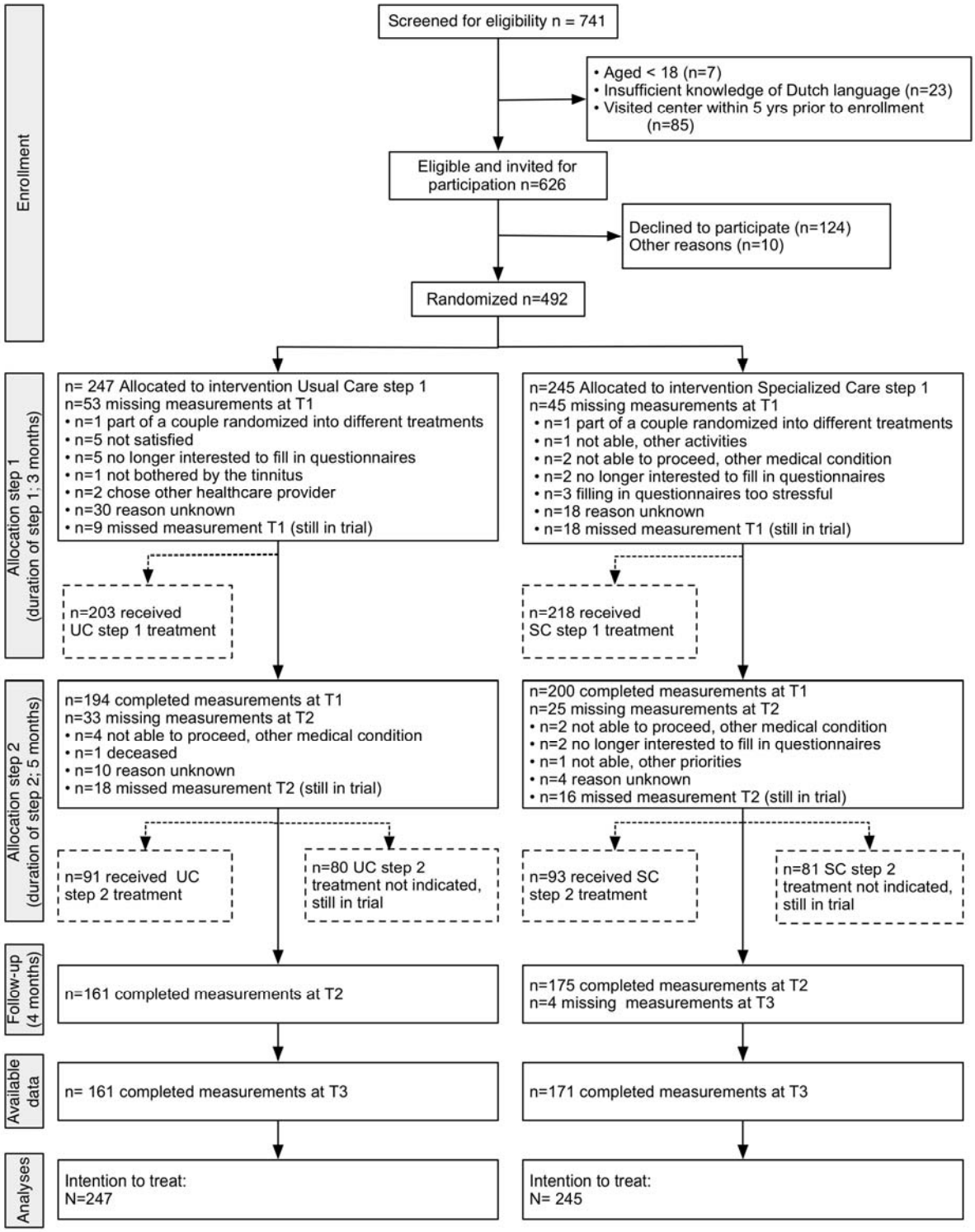
In Table 1 the sample characteristics for the total group and UC and SC separately are displayed. There were no significant differences found in demographic variables (p >.20). Participants were evenly divided among treatment condition on the basis of hearing loss as well (p =.95).

Table 1. Summary of demographic characteristic, hearing loss and baseline costs of the all participants and for the UC and SC separately

	Total (n = 492)	**UC (n = 247)**	**SC (n = 245)**	**p***
Age in yrs (SD)	54.21 (11.52)	54.60 (11.99)	53.82 (11.05)	0.45
Gender (% male)	62.8	60.7	64.9	0.38
Education (%)				0.39
Low	45.7	47.4	44.1	
Middle	27.4	24.7	30.2	
High	26.8	27.9	25.7	
Employment (% yes)	53.2	50.2	56.1	0.21
Duration (%)				0.26
Less than 1 yr	30.3	33.6	27.0	
1 to 5 yrs	38.7	37.7	39.8	
More than 5 yrs	31.0	28.7	33.2	
Fletcher index (1, 2 and 4 kHZ)	30.8	30.8	30.9	0.95
Costs $ (societal perspective)	1749	1848	1651	0.20

UC = Usual Care, SC = Specialized Care, kHZ = kilohertz

*Chi square tests (α= .05) for categorical variables, independent t-tests for continuous outcomes, Mann-Whitney U Test if data were not normally distributed.



UC = Usual Care; SC = Specialized Care; T0 = month 0; T1 = month 3; T2 = month 8; T3 = month 12

* Patients not able to enrol because of other medical issues or life events, moved to another area or started another job

Figure 1. Trial profile

Effects

Baseline utility scores were not normally distributed (p =.000, K-S test). The baseline utility scores on the HUI Mark III were 0.64 (SD=0.29) in the UC group and 0.63 (SD=0.28) in the SC group. This difference was not statistically significant (Mann-Whitney U Test; p =.503). In the base case analysis, the incremental QALY is 0.015 (Bootstrapped 95% confidence interval: -0.030 – 0.058). The data in Table 2 show that the way of handling missing values impacts the utility scores. The predicted values from the multilevel mixed regression and the complete case analysis did indicate a clinically important change in the SC group

Costs

At baseline, costs were not normally distributed (p =.000, K-S test). The total costs at baseline were $1,848 for UC and $1,651 for SC. No significant differences in costs between the groups for one of the cost categories (Mann-Whitney U Test; p >.200), or for the total costs were observed (Mann-Whitney U Test; p =.828). Table 3 summarizes the number of patients that recorded the use of the different resources at least once during the follow-up period and the mean costs per patient for each group. The mean total health-costs per patient amount to $3,875 in UC and $4,023 in SC. The costs of both first and second level tinnitus care at the audiological centre are higher in SC ($2,091 and $865 respectively) than in UC ($1,848 and $365 respectively). Other healthcare costs related to tinnitus are lower in SC. The mean total societal costs amount to $7,027 in UC and $7,380 in SC. Patient and family costs are similar in both groups. Costs of lost productivity are higher in SC. In the base case analysis, the incremental costs from a societal perspective are $357 (Bootstrapped 95% confidence interval: - $1,034 – $1,782).

Table 2. Mean utility scores measured by the HUI Mark III and QALYs for the base case analysis and sensitivity analyses that tested different ways of handling missing data.

	Base case analysis		**Sensitivity analyses**			
	Multiple Imputation		**Predicted Values from Multilevel Mixed Regression**		**Complete Cases Analysis**	
	UC	**SC**	**UC**	**SC**	**UC**	**SC**
N	247	245	247	245	130	140
baseline	0.64 (0.29)	0.63 (0.28)	0.64 (0.29)	0.63 (0.28)	0.64 (0.30)	0.65 (0.26)
3 months	0.62 (0.31)	0.62 (0.28)	0.63 (0.26)	0.63 (0.25)	0.64 (0.28)	0.64 (0.26)
8 months	0.62 (0.31)	0.64 (0.29)	0.63 (0.23)	0.66 (0.22)	0.63 (0.28)	0.68 (0.23)
12 months	0.61 (0.31)	0.65 (0.29)	0.63 (0.23)	0.68 (0.21)	0.63 (0.28)	0.69 (0.24)
QALY	0.62 (0.25)	0.64 (0.22)	0.63 (0.22)	0.65 (0.20)	0.64 (0.26)	0.66 (0.22)

HUI=Health Utilities Index, QALY=quality-adjusted life year , UC=Usual Care, SC=Specialized Care

Table 3. Total mean costs per cost item per patient in usual care (N=247) and specialized care (N=245)

Cost component	Unit costs $	Mean costs*			
		N	SC	N	UC
Healthcare costs			**4034**		**3882**
increment			***152***		
First level tinnitus care			***2091***		***1848***
Pure tone audiometry	40.48[a]	240	82.78	242	81.44
Speech audiometry	28.29[a]	240	57.86	242	56.93
Tympanometry: incl. stapdial reflexes	33.63[a]	240	68.78	242	67.68
Tinnitus analysis: PMF, MML	18.57[a]	240	37.97	242	37.36
Uncomfortable Loudness Levels	74.71[a]	240	152.78	242	150.33
Individual consult by clinical physicist in audiology	181.06[a]	240	370.24	242	364.31
Hearing aid fitting	438.22[c]	63	193.39	63	187.52
New hearing aid	1037.50[b]	46	338.78	45	315.03
Hearing aid check and optimisation	122.35[a]	90	75.41	125	107.50
Fitting tinnitus masker	438.22[d]	45	128.42	55	139.76
New tinnitus masker	1248.50[d]	37	315.95	46	323.50
BERA	190.66[a]	19	14.78	19	14.67
Intake psychologist	277.79[a]	211	239.24	1	0.81
Tinnitus Educational Group session	16.42[e]	211	14.35	2	1.12
			694		***365***
Second level tinnitus care					
Individual trajectory	434.79[e]	10	17.74	-	-
Treatment group A	1481.28[e]	41	247.89	-	-
Treatment group B	2526.18[e]	34	352.30	-	-
Social work trajectory (incl. intake)	397.26[a]	22	76.36	96	365.10
General practitioner practice			***97***		***166***
GP visit	34.96[f]	95	50.20	129	84.57
GP home visit	53.69[f]	45	21.61	65	38.79
GP assistant visit	17.48[f]	62	13.28	76	21.66
GP weekend and evening	74.36[g]	22	12.76	32	21.11
Hospital care			***479***		***562***
ENT specialist visit	161.06[f]	95	215.40	117	240.56
Neurologist visit	161.06[f]	37	52.03	45	67.56
Dental surgeon visit	161.06[f]	14	16.95	19	27.82
Other medical specialist	161.06[f]	55	195.28	79	226.30
Other healthcare professionals			***674***		***941***
Physiotherapist	44.95[f]	104	151.24	122	224.29
Psychologist	213.49[f]	74	149.42	94	227.64
Psychiatrist	161.06[f]	42	60.02	53	73.34
Social worker	81.15[f]	48	39.53	74	60.19
Occupational therapist	27.47[f]	19	4.88	30	10.25
Company doctor	161.06[f]	79	179.72	87	207.96
Homeopath	12.49 – 103.00[h]	54	24.61	67	42.14
Acupuncturist	24.97 – 116.53[h]	54	28.50	71	41.30
Haptonomist	15.61 – 49.94[h]	36	5.28	48	14.82
Magnetizer / Faith healer	34.96 – 62.43[h]	38	1.15	45	2.90
Prescribed medication					
Medication	Various[b]	79	29.40	84	36.43

Patient & family costs			***106***		***135***
Over the counter medication	Various[h]	78	6.18	84	10.21
Traveling expenses	Various[h]	138	4.51	153	5.71
Sports, meditation or other costs	6.24 - 1198.20[h]	112	95.77	119	119.61
Productivity losses			***3252***		***3018***
Loss of productivity at paid labour	Mean /hour[f]	128	3252.14	128	3018.16
Total societal costs			**7392**		**7035**
increment			***357***		

* Missing value analysis based on multiple imputation
PMF = Pitch Match Frequency; MML = Minimum Masking Level
[a] Anonymous source; [b] GIP databank 2009; [c] www.nvab.nl; [d] oral communication with several hearing aid dispensers; [e] cost calculation; [f] Hakkaart et al. 2010; [g] www.nza.nl/regelgeving/tarieven; average tariff 2009 calculated for Limburg; [h] cost questionnaire.

Cost-effectiveness

In the base case analysis the mean incremental cost-effectiveness ratio amounts to $10,456 per QALY gained from a healthcare perspective, and $24,580 per QALY gained from a societal perspective (Table 4). Based on these results, SC can be considered cost-effective as opposed to UC. The sensitivity analyses show slightly more beneficial results. When using the predicted values from the mixed regression to handle missing values in the HUI scores, the incremental cost-effectiveness ratios are slightly lower. In the complete cases analysis the incremental cost-effectiveness ratio is lower from a healthcare perspective, but higher when adopting the societal perspective.

In the analyses conducted from a societal perspective, the uncertainty surrounding the incremental costs and effects is considerable (Figure 2). From a healthcare perspective, especially the uncertainty surrounding the incremental effects are considerable (Figure 3). In the base case analysis, from the healthcare perspective the probability that SC is cost-effective is 68% for a willingness-to-pay for a QALY of $45,000 (Figure 4). From the societal perspective, the probability that SC is cost-effective is 58% for a willingness-to-pay for a QALY of $45,000 (Figure 4). The sensitivity analyses show slightly more favorable results for SC, except for the complete cases analysis from a societal perspective for which the probability that SC is cost-effective is 52% for a willingness-to-pay for a QALY $45,000 (Appendix A).

Table 4. Results of the cost-effectiveness analysis from the healthcare and societal perspective for the base case and two sensitivity analyses.

Analysis		Increments	Uncertainty				
		Mean/ patient	Bootstrap 95% CI	Distribution on the cost-effectiveness plane			
				NE	SE	SW	NW
Base case analysis Multiple imputation	**Healthcare Costs**	$ 152	$ -333 to $ 643				
	QALY	0.0145	-0.028 to 0.055				
	iCER	$ 10,456		52%	22%	4%	22%
	Societal Costs	$ 357	$ -1,034 to $ 1,782				
	QALY	0.0145	-0.028 to 0.055				
	iCER	$ 24,580		48%	20%	6%	27%
Sensitivity analysis I QALY based on predicted values of MMR used in the effectiveness paper	**Healthcare Costs**	$ 152	$ -333 to $ 643				
	QALY	0.017	-0.019 to 0.057				
	iCER	$ 9,200		60%	13%	6%	21%
	Societal Costs	$ 357	$ -1,034 to $ 1,782				
	QALY	0.017					
	iCER	$ 21,628		55%	13%	6%	21%
Sensitivity analysis II Complete cases analysis	**Healthcare Costs**	$ 288	$ -320 to $ 883				
	QALY	0.029	-0.028 to 0.080				
	iCER	$ 10,069		68%	15%	1%	16%
	Societal Costs	$ 1,001	$ -941 to $ 2,983				
	QALY	0.029	-0.028 to 0.080				
	iCER	$ 35,009		67%	15%	1%	17%

CI = Confidence Interval, MMR = Mixed Multilevel Regression, QALY = quality-adjusted life year, iCER = incremental Cost Effectiveness Ratio

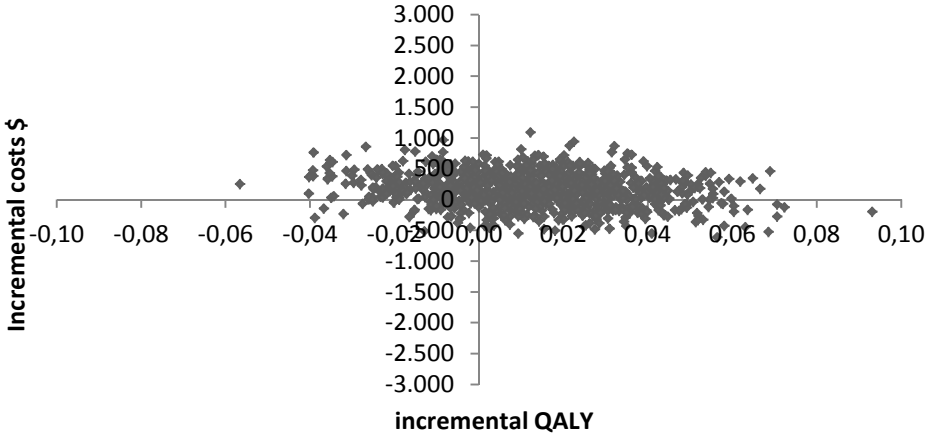


Figure 2. Cost-effectiveness plane of base case analysis from healthcare perspective

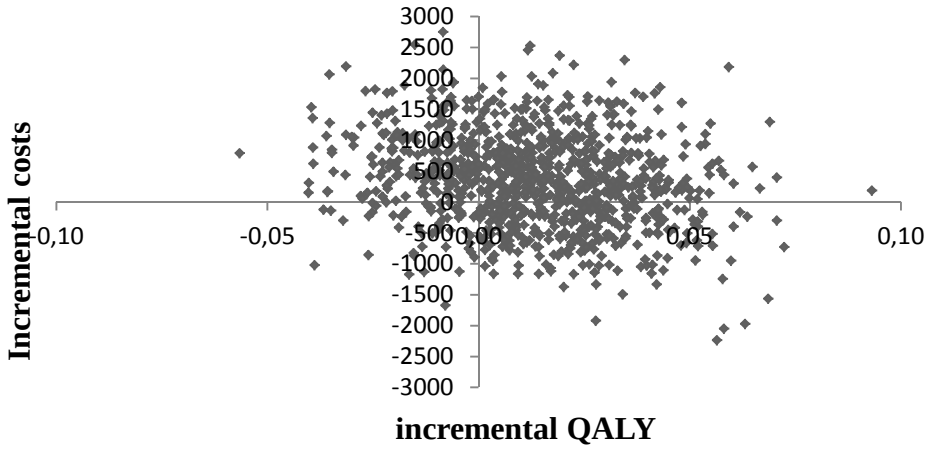


Figure 3. Cost-effectiveness plane of base case analysis from societal perspective

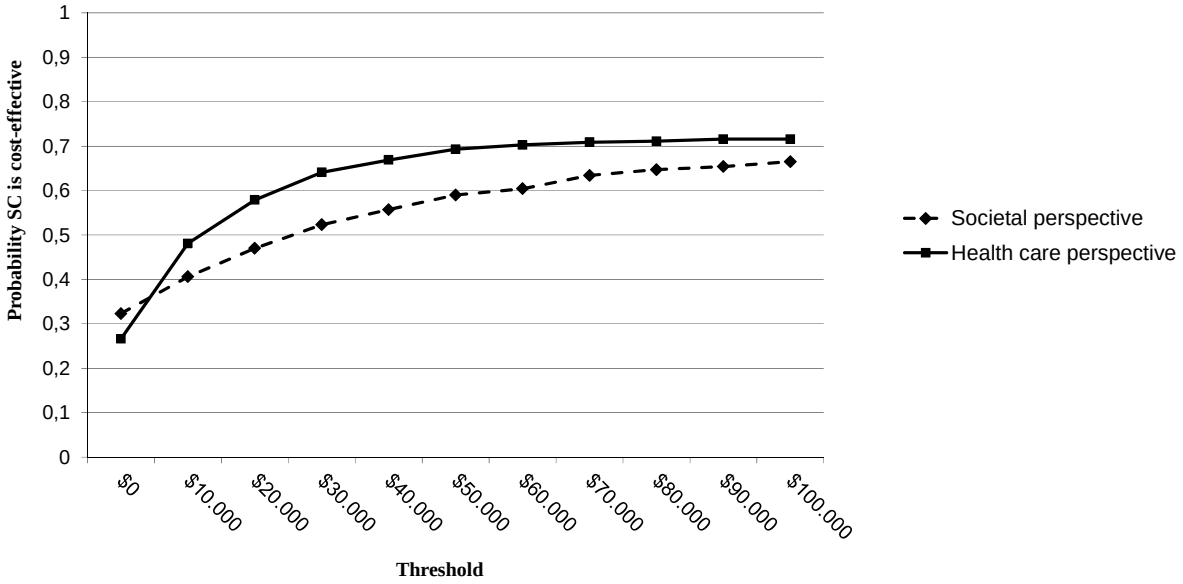


Figure 4. Cost-effectiveness acceptability curves of the base case analysis

Discussion

This article reports on what is, to our knowledge, the first full economic evaluation of a multidisciplinary stepped care approach to tinnitus treatment combining TRT and CBT. In the clinical effectiveness study of this trial it was shown that there was a significant improvement in quality of life (Cima et al., 2012). Other studies found that treatments based on TRT or CBT, which were an important part of the SC, were effective up to 15 years after the therapy ended (Forti et al., 2009; Goebel et al., 2006; Lux-Wellenhof & Hellweg, 2002; Zachriat & Kroner-Herwig, 2004). It would be interesting to know the longer term effects of SC and UC on health-related quality of life. Costs associated with the tinnitus care in the audiological centre were considerably higher in SC. This was partly compensated by lower costs in SC for other tinnitus related healthcare costs. Productivity costs were higher in SC. This could be due to the fact that the SC is more time-consuming than the UC. Participants with paid jobs in one of the treatment groups of SC, were often absent from work during the treatment days.

Moreover, in second level tinnitus care in SC it is advised to participants to, if on sick leave, resume their paid work only after the intervention is completed. With regard to cost-effectiveness, the results show that SC costs society $24,580 per QALY gained based on the base case estimates of input parameters. Although there is no consensus about a reasonable threshold value for cost-effectiveness, the NICE guideline state that the reimbursement of interventions costing less than £30,000 (approximately $46.453) are generally never questioned (Devlin & Parkin, 2004; Raftery, 2001). The Dutch Council for Public Health and Health Care has set the threshold at €80.000 (approximately $99,880) for diseases with a high burden (RVZ, 2006). The low quality of life scores at baseline (0.63) indicate that tinnitus is a relatively high burden to the patients that suffer from it. Therefore we consider the treatment to be cost-effective, despite the uncertainty surrounding the incremental costs and effects was substantial, mainly for the analyses from a societal perspective. If willingness-to-pay for an additional QALY amounts to $100.000, the probabilities that SC is the most cost-effective treatment are 67% (societal perspective) and 72% (healthcare perspective). Sensitivity analyses showed that the approach to handling missing values impacted on the results. However, it did not alter the conclusions.

Some limitations of this study need to be considered. First, the proportion of missing data and non-response was acceptable, however larger than expected. In the base case analysis it was assumed that data were missing at random but, at this level of missing data, we cannot rule out the possibility of non-random causes for dropout. Fortunately, the sensitivity analyses show that, although the approach to handling missing values does impact the results, the conclusions remain the same. Second, a longer time horizon may be necessary to identify relevant longer-term outcomes; especially since quality of life slightly improves at the last follow-up in the SC, and deteriorates in the UC. It is expected that a longer time horizon would show even more favorable results for the SC. Third, because SC had several elements it is unclear which of these elements contributed to the overall effectiveness. A dismantling approach in which potentially redundant factors are left out are expected to result in a more cost-effective treatment.

In conclusion, this economic evaluation, conducted from a societal perspective using a one year follow-up period, shows that a specialized multidisciplinary tinnitus treatment based on cognitive behavioral therapy may be more cost-effective than usual care.

Acknowledgements

We thank all professionals, support staff, and management of Adelante, Department of Audiology and Communication for enabling the randomized controlled trial; all participating patients with tinnitus; Marieke Jansen, Lobke Dauven, Pauline Cox and Martijn van Veghel (Adelante Department of Audiology and Communication, Hoensbroek, Netherlands) for randomization, organization of off-centre contacts, data entry, and data management; Rosanne Janssen (Maastricht University, Maastricht, Netherlands) for assisting with the online application

Emium; Maastricht University Medical Centre, department of clinical epidemiology and MTA and Maastricht University, Faculty of Psychology and Neuroscience, for all supporting services.

Appendix A. Results of sensitivity analysis

Sensitivity analysis I

Figure 1. Cost-effectiveness plane from the societal perspective of sensitivity analysis in which missing values on HUI were based on predicted values from multiple mixed regression in the clinical effectiveness analysis

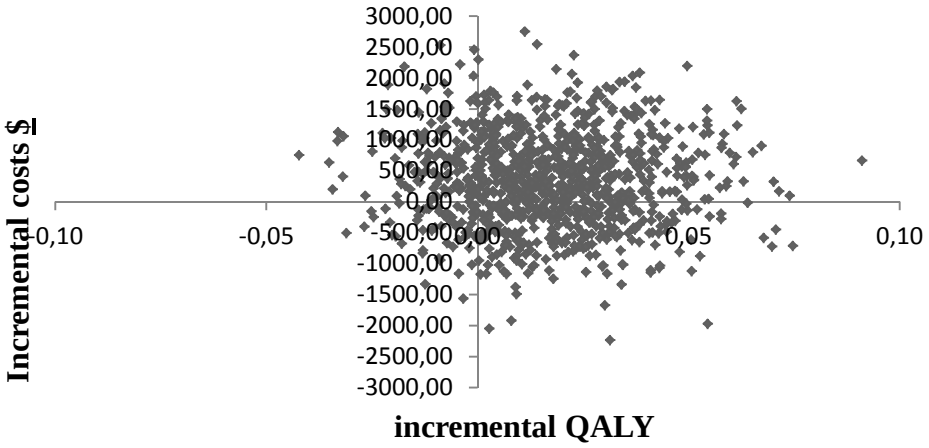


Figure 2. Cost-effectiveness plane from healthcare perspective of sensitivity analysis in which missing values on HUI were based on predicted values from multiple mixed regression in the clinical effectiveness analysis

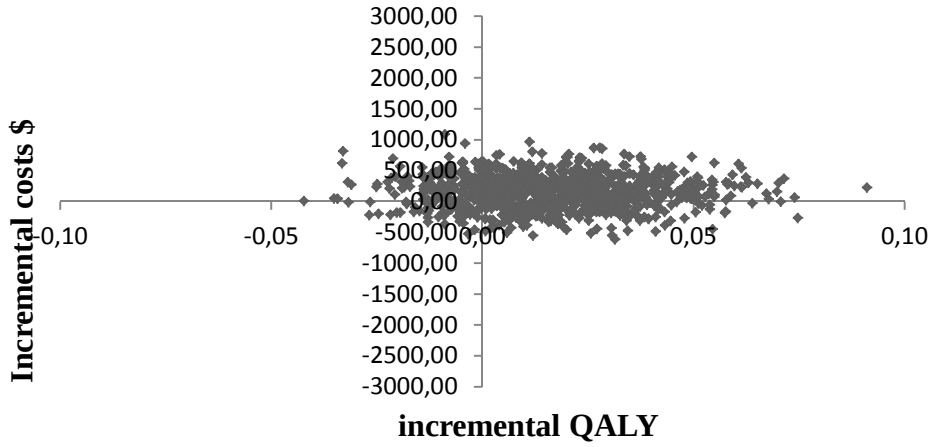
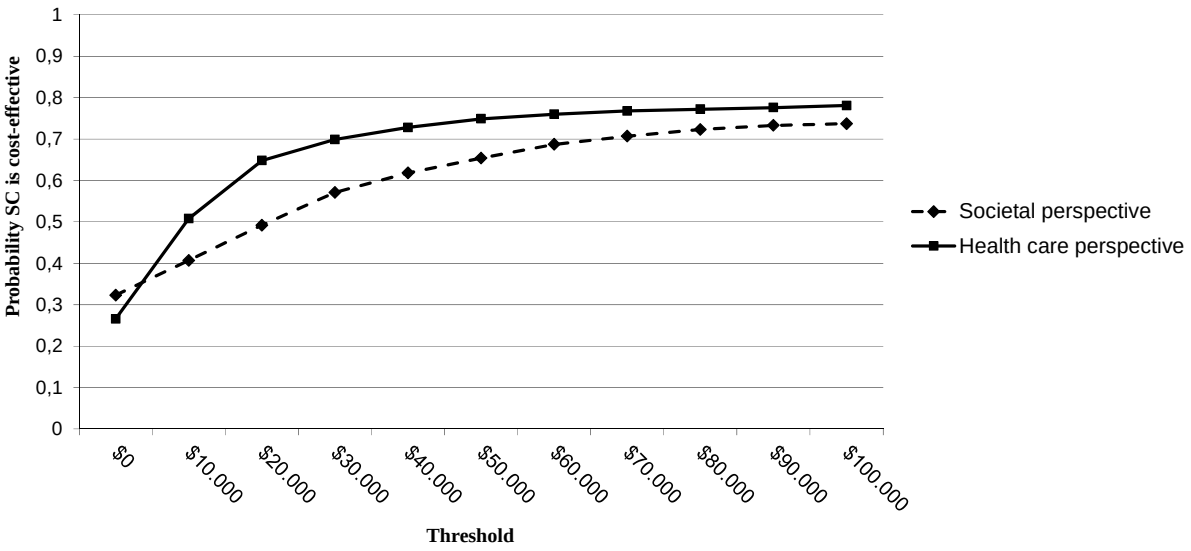


Figure 3. Cost-effectiveness acceptability curves based on sensitivity analysis in which missing values on HUI were based on predicted values from multiple mixed regression in the clinical effectiveness analysis



Sensitivity analysis II

Figure 4. Cost-effectiveness plane from societal perspective of complete cases analysis

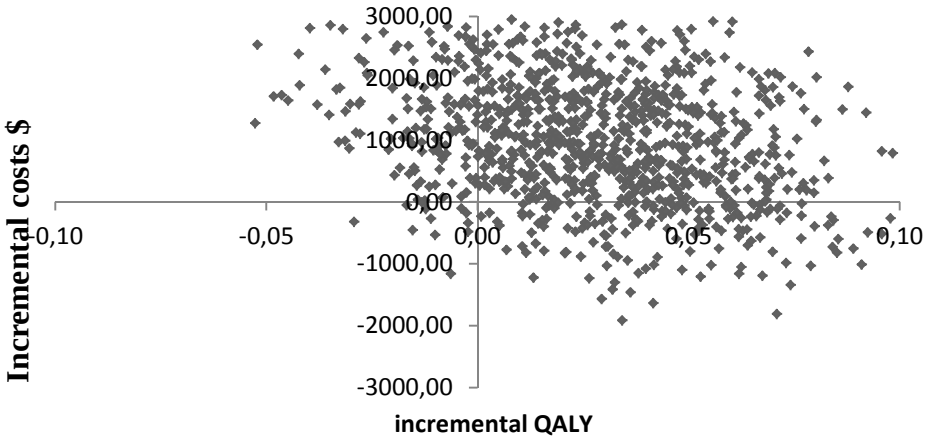


Figure 5. Cost-effectiveness plane from healthcare perspective of complete cases analysis

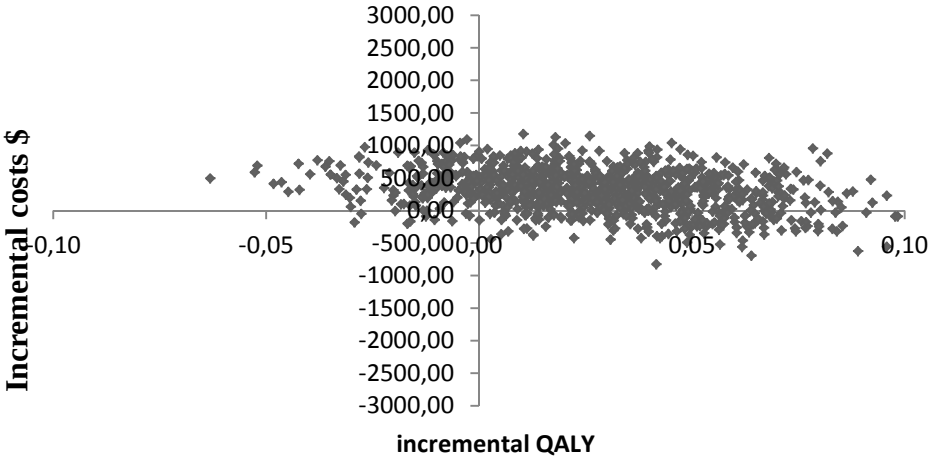
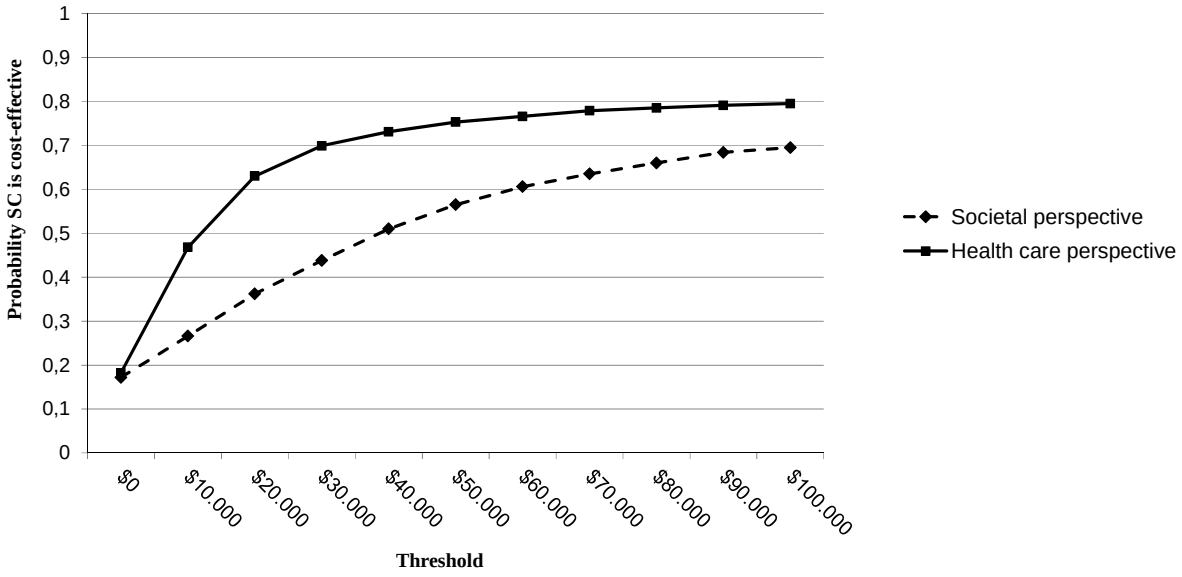


Figure 6. Cost-effectiveness acceptability curves based on complete cases analysis



CHAPTER 5

Measuring health-related quality of life by experiences: the Experience Sampling Method

Iris H.L Maes, Philippe A.E.G. Delespaul, Madelon L. Peters, Mathew P. White, Yvette van Horn, Koen Schruers, Lucien J.C. Anteunis, Manuela A. Joore

Submitted for publication

Abstract

Objectives To explore the potential value of obtaining momentary, instead of retrospective, accounts of the description and valuation of a person's own health-related quality of life (HRQOL).

Methods Momentary HRQOL was examined with the Experience Sampling Method (ESM) in 139 participants from 4 different samples. The ESM consists of a beep questionnaire that was administered 10 times a day. Feasibility of was determined by assessing willingness to participate in the study and by analyzing the percentage of drop-outs and the number of completed beep questionnaires. Bivariate correlations and multilevel analysis were used to investigate the relation between momentary HRQOL and momentary feelings and symptoms. The relation between momentary outcomes and the EQ VAS was investigated with a multiple regression model.

Results The overall participation rate was low but there were no drop-outs and the number of completed beeps was comparable to other studies. Multilevel analysis showed that feelings and symptoms were significant predictors of momentary HRQOL. The strength of these relations differed between the groups. The EQ VAS was not predicted by momentary feelings, symptoms and HRQOL.

Conclusion We can conclude that the use of the ESM to measure accounts of the momentary experience of health in different populations is feasible. Retrospective measures may provide a biased account of the impact of health problems in the daily lives of people who are affected. Moreover, the bias may be different in different conditions.

Introduction

The quantification of the subjective experience of health, or health-related quality of life (HRQOL), outcome is crucial to the evaluation of health care technologies. To assign meaningful numbers to health outcomes, the experience needs to be described in terms of severity, and assigned a value. Instruments to obtain patient descriptions and valuations of their own health, such as the EQ-5D health description and visual analogue scale (EQ VAS), rely on retrospective self-report. A problem with retrospective self-report is that it is likely to give a biased account of real-world experiences due to imperfect recollection of past experiences (Reis, 2012; Stone & Shiffman, 2002). In other words, it does not reflect the impact of health problems in the daily lives of people who are affected. An alternative to retrospective self-report, is to study outcomes from moment to moment, in the context of daily life. The objective of the present study was to explore the potential value of obtaining momentary, instead of retrospective, accounts of the description and valuation of a person's own health.

Retrospective versus momentary self-report

Robinson & Clore (2002) reviewed several studies describing discrepancies between momentary and retrospective self-reports. Retrospective self-reports are not accurate reflections of experience because feelings are not always accurately represented in memory. If not measured directly, the affective experience needs to be reconstructed on the basis of episodic or semantic memory. Episodic memory is the recollection of past personal experiences that occurred at a particular time and space. Semantic memory is a more structured record of facts and knowledge about the external world that is independent of personal experience. With regard to episodic memory, Kahneman et al. (1993) found that more memorable moments or details of an emotional event disproportionately affect retrospective estimates of emotion. It also has been shown that there is a gradual decline in episodic memory (Rubin & Wetzel, 1996), which leads to a reliance on semantic memory to fill in the memory gap of hedonic experience (or experiential knowledge). Semantic memory relies more on generalized beliefs than on experiences. In this regard, there is a distinction between retrospective self-reports of global concepts and retrospective self-reports of specific feelings and symptoms. Global reports of past health will rely more on beliefs (semantic memory), while reports on specific feelings and symptoms may more easily be recovered by detailed episodic recall (Kahneman et al., 2004; Robinson & Clore, 2002; Stone et al., 2006). As a result, the retrospective global valuation of health may be more prone to bias than the retrospective description of detailed aspects of health such as specific feelings or symptoms. Methodological literature on self-report measures has highlighted that many of the problems described above will be reduced when questions are asked in close temporal proximity to the event of interest (Schwarz, 2011). More fundamentally, there is an increasing awareness that experiences are dynamic, situated, and highly context driven (see the contributions in Mesquita, Barrett, & Smith, 2010) thereby providing a powerful rationale for investigating experiences in the context in which they occur (Robbins & Aydede, 2008). It could be that bias in retrospective self-report is different in different patient populations. For instance, depression has been shown to have an effect on memory performance (Burt et al., 1995; Kizilbash et al., 2002). In addition, feelings are fleeting and thus not available through introspection once the feeling dissipated. Therefore, retrospective reports of affective experiences may be especially prone to bias. As a result, a higher discrepancy between retrospective self-report and actual experiences may occur in persons suffering from psychological complaints. It is also well know that people do not adapt well to the presence of noise (Loewenstein & Schkade, 1999; Weinstein, 1992). This could mean that patients with a complaint like tinnitus, which is the experience of a sound without an acoustic source, or pain

disproportionately focus on this aspect when evaluating their health-related quality of life retrospectively.

Experience Sampling Method
In the present study we used a real-time method, the Experience Sampling Method (ESM) (Larson & Csikszentmihalyi, 1983), to obtain momentary accounts of feelings, physical symptoms and HRQOL. The ESM was developed in the 1970s. It is characterized by the collection of multiple self-reports of an individual's (near) real-time feelings, thoughts and activities in real-world environments. ESM studies are conducted using paper diaries or (increasingly) electronic devices (Trull & Ebner-Priemer, 2009). These devices beep at random moments, when participants are asked to complete a questionnaire. A potential limitation of the ESM is that it can be time consuming and intrusive, and as a result burdensome to participants (Conner et al., 2009).

Objectives
In this study, first we assessed the feasibility of using the ESM to obtain accounts of the momentary valuation of HRQOL in different patient populations. Next, it was hypothesized that if the momentary valuation of HRQOL would vary over time, this would be an indication that the momentary valuation of a global concept like HRQOL is influenced by the momentary experience of more specific feelings and symptoms. Therefore, we assessed whether the momentary valuation of HRQOL is variable from moment to moment within persons. Furthermore, we examined the relation between momentary accounts of specific feelings and symptoms and the momentary valuation of HRQOL. Finally, we examined the relation between the global retrospective valuation of HRQOL (as obtained by the EQ VAS) and the momentary accounts of feelings and symptoms and valuation of HRQOL.

Methods

Study population

The study population consisted of 139 participants. To ensure a variety of experienced health states in the study population, participants were recruited from three patient groups (experiencing somatic complaints with a known cause, somatic complaints without a known cause, and psychological complaints) and a population based sample. All participants were 18 years or older. Exclusion criteria were not being able to read and write in Dutch or not being able to handle the electronic ESM device because of impaired motor skills.
The population based sample consisted of members of the general public. These participants were recruited through advertisements/posters in the Maastricht University Hospital.
The patient group with psychological complaints consisted of patients with anxiety or depressive complaints. Specific inclusion criteria for this sample were a referral to a mental health care setting because of anxiety or depressive complaints, or a score of >8 points at either the anxiety or depression scale, or >12 points on the total score of the Hospital Anxiety and Depression Scale (Spinhoven et al., 1997). This group was interesting, as noted above, because there may be larger discrepancies in momentary versus retrospective assessments. These patients were recruited from PsyQ Maastricht, a secondary mental health care facility. During the intake the psychologist introduced the study, and patients were asked whether they agreed to being approached. Patients in this sample were also recruited by flyers in several mental health care centres and an advertisement in a local newspaper.
The group of patients with somatic complaints without a known cause consisted of patients with tinnitus. As noted above people find it difficult to adapt to noise so this was a particularly interesting group. A specific inclusion criterion for this sample was referral to an audiological centre because of tinnitus complaints. Specific exclusion criterion was an organic

cause of the tinnitus. These participants were recruited from a completed randomized controlled trial investigating the (cost-)effectiveness of a multidisciplinary treatment for tinnitus versus care as usual (Cima et al., 2009; Cima et al., 2012). Participants in the vicinity of the Maastricht University Medical Centre received a letter in which their participation was requested.
The group of patients with somatic (bodily) complaints with a known cause consisted of patients diagnosed with atherosclerosis or venous insufficiency. In instances where patients underwent a leg amputation as a result of these complaints, the clinical rehabilitation had to be finished before participating in the trial. Participants were recruited from Adelante, a centre of expertise in rehabilitation and audiology and the department of surgery from the Maastricht University Medical Centre. The treating physician introduced patients to the study and asked whether they would be interested to learn more about participating in the study from the research team.
All potential participants received written information. If they were willing to participate in this study they returned the informed consent by mail. The study protocol was reviewed and approved by the Medical Ethical Board of the Maastricht University Medical Centre.

Measures

Experience Sampling Method using the Maastricht routine described by Delespaul (1995).
The ESM consists of a beep questionnaire that participants are required to fill out at several unpredictable moments during the day. They will also have to answer additional question in the morning when they wake up and in the evening when they go to sleep. The validity and reliability of the Maastricht routine has been documented elsewhere (Delespaul, 1995). In this study we used the PsyMate, a small user-friendly device programmed to generate beeps (and vibrations) between 07.30h and 22.30h randomly in two-hour intervals. The beep questionnaire consists of 11 items on current emotional state; six for positive affect (PA) and five for negative affect (NA). Four items were included to measure physical symptoms. Contextual items, regarding location of the participants, social interactions and activities were also included in the beep questionnaire. Items on activities and social interaction consisted of predetermined categories (see Appendix A). For all remaining items a 7-point Likert-scale was used. 5- or 7-point Likert-scales are most commonly used, but a 7-point Likert scale has greater potential sensitivity (Colman et al., 1997). To measure the meaningfulness of the (social) activities, again a 7-point Likert-scale was used. To obtain a valuation of momentary HRQOL, a VAS anchored in the same way as the EQ VAS (0 being the worst imaginable health state and 100 being the best imaginable health state) was included in the beep questionnaire (The EuroQol Group, 1990). Items were formulated to be as neutral as possible in order to minimize framing effects. So, for instance, questions such as ‘are you bothered by (e.g. pain)’, that can be considered leading, were replaced with items that ask people to simply state a) how much pain they are in and b) how frustrated/sad they are at the moment. By analyzing the co-occurrence of emotional states we can draw conclusions about the degree to which the existence of pain is related to emotional well-being. In terms of question order, respondents were asked to comment on their emotional states before being asked about what they were doing or who they were with to reduce potential focusing effects (appendix A). In total 37 items were included in the ESM beep questionnaire. The average time to complete the questionnaire was between 2 and 3 minutes.

Global measures
Global retrospective valuation of health, or HRQOL as measured with the EQVAS (24);
- Anxiety and depression as measured with the Hospital Anxiety and Depression Scale (HADS) (19);

- A questionnaire on personal characteristics.

Data collection

The study consisted of three phases planned individually for each participant. All participants received € 25 for their participation.

Briefing session

Day 1 consisted of a briefing and collection of baseline global data, and took around 3 hours per participant. During the briefing the rationale of the study was explained and an instruction on the use of the PsyMate was given. A try-out sampling moment was simulated in which the participants were coached in answering the questions on the PsyMate. After the try-out the EQ VAS, the HADS and the questionnaire on personal characteristics were administered.

ESM period

The ESM period comprised 6 days, starting the day after the briefing and ending the day before the debriefing a week later. During this week the participants were asked to continue their normal life. Additional questions had to be answered in the evening just before they went to sleep (end-of-day questionnaire).

Debriefing

On the 8th day participants returned for a debriefing session. In this session the ESM period was reviewed by means of a questionnaire. In this questionnaire participants had to answer whether the PsyMate had influenced their mood, activities, thoughts or contacts with other people and if they had been annoyed by the beeps. Furthermore participants were asked whether the ESM week had been a typical week or if any unusual incidents had occurred, if items were unclear and if they thought they could give a good representation of their experiences during the day. The EQ VAS, and the HADS were administered again.

Analyses

Feasibility

To determine the willingness to participate in an ESM study, in the patient samples the number of participants that was approached for participation was compared with the number of participants that actually participated in the study. For both the patient samples and the population based sample the percentage of dropouts was recorded and analyzed. Furthermore, we assessed the feasibility by analyzing the number of completed beep questionnaires. Also the responses to the debriefing questionnaire were analyzed.

Construction of scales

Appendix A gives an overview of the items in the ESM. A principal components exploratory factor analysis on positive and negative affect (PA & NA) items and physical symptoms (PS) was used to examine the underlying factor structure (White & Dolan, 2009). A principal components exploratory factor analysis on these items confirmed a three factor solution. To aid the interpretation of these three components, a non-orthogonal (oblique) solution was used. The 6 items on positive affect loaded onto the first factor (Eigen value = 3.547; variance explained 23.6%; all item factor loadings > .643). A positive affect (PA) scale was created by calculating the mean of these items. The 5 items on negative affect loaded onto the second factor (Eigen value = 1.330; variance explained 8.9%; all item factor loadings > .408). We created a negative affect (NA) scale by calculating the mean of these five items. The four physical symptom items loaded onto the third factor (Eigen Value=1.229; variance

explained=8.2%: all item factor loadings >.384). We created a physical symptoms (PS) scale by calculating the mean of these four items.

Variability of the momentary valuation of HRQOL within and between persons.
To determine if there was variability in the momentary valuation of HRQOL within persons, for each respondent a standard deviation (SD) was determined over the responses to the beep questionnaires. A histogram of the different SD's was made to display the differences between persons. In addition, a repeated measures ANOVA with a Greenhouse-Geisser correction was used to explore whether the variability in valuations differed over the days in the ESM week. A linear regression was used to examine the relation between mean HRQOL and mean SD of HRQOL.

Relation between the momentary valuation of HRQOL and the simultaneous experience of feelings and symptoms.
Bivariate correlations between the momentary valuation of HRQOL and PA, NA and PS for each participant were computed and displayed in a histogram. Correlations were interpreted according to the following benchmarks: 0.1 to 0.3 was interpreted as small, 0.3 to 0.5 as medium and >0.5 as large (Cohen, 1988). To examine whether momentary feelings and symptoms predict the momentary valuation of HRQOL a multilevel random regression model was estimated with the momentary HRQOL as the dependent variable and momentary PA, NA and PS as independent variables. A multilevel (or hierarchical) regression analysis is ideally suited for data obtained with the ESM since beep level data (level 1) are nested within persons (level 2). In multilevel analysis a curve is fitted for the dependent variable for each participant, thereby taking into account the fact that beep-level measures of within patients measures tend to be more alike than randomly chosen beep level measurement. All multilevel analyses were computed with the XTMIXED modules of STATA 11.0. Since different scales were used, all variables were standardized. The analyses were corrected for age, sex and group difference by including three dummy variables for the different groups. Group was entered in the mixed regression as a categorical variable using dummy coding with the general population sample as a reference category and a dummy indicator for every other group[4]. The general population sample was treated as the reference group. To determine the explained variance of PA, NA and PS separately, these variables were first added separately to the basic model (which included momentary HRQOL and the covariates). A final model was fitted with the momentary HRQOL as dependent variable and momentary PA, NA, PS and their interaction with the dummy variables as independent variables. We expected a positive relation between PA and HRQOL, and a negative relation between NA and PS and HRQOL.

Relation between the EQ VAS and momentary HRQOL, feelings and symptoms.
Aggregated means and standard deviations of momentary HRQOL, PA, NA and PS were calculated and compared with the EQ-5D VAS at briefing and debriefing. This was done for the total group and for all four subgroups. Furthermore, correlations between momentary HRQOL, PA, NA and PS on the one hand and the retrospective valuation of HRQOL (EQ VAS) on the other hand were computed. Correlations were interpreted according to the same benchmarks as mentioned in the previous paragraph. To examine how much of the variance in the EQ VAS at debriefing was explained by momentary PA, NA, PS and momentary HRQOL a multiple regression model was fitted to the aggregated data. All the variables were

[4] Dummy 1: 1=Psychological complaint sample, 0=Tinnitus sample, 0=Somatic complaints sample. Dummy 2: 1=Tinnitus sample, 0= Psychological complaint sample, 0=Somatic complaints sample. Dummy 3: 1=Somatic complaints sample, 0=Tinnitus sample, 0=Psychological complaint sample

standardized. The EQ VAS at debriefing was the dependent variable and momentary PA, NA, PS and HRQOL were the independent variables. Age, sex, EQ VAS at briefing and sample (by including three dummy variables with general population as reference group) were taken into account as covariates.

Results

Feasibility

Demographic characteristics of the total sample and sub-samples are displayed in table 1. Mean age of the total sample was 50 years and 50% was male.

Table 1. Demographic characteristics of the participants

Characteristics	Total sample	General population	Psychological complaints	Tinnitus	Somatic complaints
N	139	40	27	40	32
Age (SD)	50.2 (16.7)	38.6 (14.6)	38.4 (12.7)	58.2 (10.0)	64.8 (10.4)
Sex (% male)	69 (49.6)	29 (72.5)	12 (44.4)	11 (27.5)	17 (53.1)
Living situation (% alone)	42 (30.2)	13 (32.5)	11 (40.7)	4 (10.0)	14 (43.8)
Education (%)					
Low	34 (24.5)	4 (10.0)	2 (7.4)	14 (35.0)	14 (43.8)
Middle	53 (38.1)	9 (22.5)	15 (55.6)	14 (35.0)	15 (46.9)
High	52 (37.4)	27 (67.5)	10 (37.0)	12 (30.0)	3 (9.4)

SD = standard deviation

Population based sample. With regard to the population based sample, 44 subjects responded to the poster and received the information on the study. Four persons declined participation after they received the information. One person found the study too burdensome and one person had a bad experience in another study. Two persons did not respond to the information letter and could not be reached by phone. In this sample 26 participants reported no physical conditions and 36 reported no psychological complaints. Physical conditions included asthma (4), back pain (3), hearing impairment (2), vision impairment (1), back pain (3), high blood pressure (2), arthritis (2), arthrosis (2), bladder carcinoma (1) and stroke (2). Four participants reported more than 1 condition. Psychological complaints included: eating disorder, burn-out (2), depressive complaints (1).

Psychological complaints sample. The information on the study was sent to 59 patients with anxiety or depressive complaints and 36 were willing to participate. Two patients did not meet the inclusion criteria. Reasons for not participating were not interested in study objective (N=2), too burdensome (N=8), not able to combine with work (N=6), transportation problems (N=2). Five patients did not respond to the information letter or telephone calls. Six patients did not show up at the briefing or cancelled their participation before the briefing. One patient was irritated by the questions in the PsyMate during the try-out sampling moment, resulting in a final sample of 27 (or 46% of those originally approached).

Tinnitus sample. For the sample of tinnitus patients, the study information was sent to 326 patients who had previously participated in a randomized controlled trial (20, 21). Forty-five patients were willing to participate in this study. Reasons for not participating were not interested in study objective (N=80), too burdensome (N=27), not able to combine with work

(N=21), other health complaints (N=20), no more tinnitus complaints (N=8), distance to research centre (N=9), afraid that attention to tinnitus during ESM week would make complaints worse (N=8). Hundred-seven patients (35%) did not respond to the information letter or telephone calls. Of 45 patients that were willing to participate, four did not come to the briefing or cancelled their participation before the briefing. One patient was not able to read the PsyMate because the font size was too small. In other words, only 14% of tinnitus patients approached, were willing or able to take part in this ESM study.

Somatic complaints sample. For the group of patients with atherosclerosis or venous insufficiency, the information was sent to 121 patients. Forty-four patients were willing to participate. Reasons for not participating were too burdensome (N=27), not interested in study objective (N=18), not satisfied with the treatment (N=2), other physical complaints (N=8), distance to research centre (N=3), not meeting inclusion criteria (N=5), no more complaints (N=2), not able to combine with work (N=1), already participating in another study (N=2). Nine patients did not respond to the information letter or telephone calls. Of the 44 patients that were willing to participate 10 patients did not show up at the briefing or cancelled their participation before the briefing. One patient cancelled participation during the briefing because the font size was too small and another person cancelled because the PsyMate made her nervous. The final sample was thus 32 (26% of those originally approached).

All participants that finished the briefing completed the ESM week. Participants responded to 5994 of the 8340 possible beeps (72%). On average participants responded to 7.2 beeps per day with a minimum of zero and maximum of 10. Over the six days the total mean number of beeps recorded per patient was 43.1 with a minimum of 17 and a maximum of 59. The majority (76%) of participant's thought of their week as being representative of a normal week and only twenty percent reported the occurrence of unusual incidents. Twenty-two percent of participants found the PsyMate annoying, ranging from nineteen percent in the psychological complaints sample to twenty-eight percent in the population based sample. In all the sub-samples more than ninety percent of the participants reported that the PsyMate did not influence their mood, social interactions or activities. Seventy-five percent of the participants reported that the PsyMate did not influence their thoughts, ranging from sixty-three percent in the psychological complaints sample to eighty percent in the tinnitus sample. The large majority of the participants (92%) reported that they were able to give a good representation of their experiences during the day. Fourteen percent of the participants found some of the questions unclear.

Variability of the momentary valuation of HRQOL within and between persons

In Table 2 the aggregated means and SD of momentary HRQOL for the total group and the subgroups are displayed. The SD's of momentary HRQOL per participant are displayed in Figure 1. The mean of the within person SD's was 5.64, with a range from 0.94 to 18.22. The mean SD at day 1 was 5.2 and decreased to 3.9 at day 6. A repeated measures ANOVA determined there was a statistically significant difference between the mean SD's over the 6 days ($F=3.545$, $df=4.417$, $p=.005$). Post-hoc tests using the Bonferroni correction revealed there only was a statistically significant difference between day 1 and day 6. In participants with a higher mean momentary HRQOL, there was less variance in responses than in participants with a lower momentary HRQOL (Figure. 2). This relation was confirmed by a linear regression that showed a significant negative relation of the mean and SD of the momentary HRQOL per participant ($\beta=-0.388$; $p=0.000$; $R^2=0.150$).

Table 2. Descriptive of momentary outcomes and global retrospective EQ VAS at briefing and debriefing

	Total	General population	Psychological complaints	Tinnitus	Somatic complaints	P-value*
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Retrospective at briefing						
EQ-5D VAS	72.85 (19.4)	88.25 (10.4)	61.26 (16.6)	69.50 (19.4)	67.56 (19.1)	.000
Momentary						
HRQOL	70.16 (17.4)	81.05 (13.8)	59.39 (16.22)	67.44 (18.3)	69.03 (14.1)	.000
Positive affect	4.67 (1.5)	5.19 (1.1)	3.51 (1.5)	4.70 (1.5)	4.89 (1.3)	.000
Negative affect	1.66 (1.1)	1.33 (0.6)	2.52 (1.3)	1.63 (1.1)	1.45 (0.8)	.000
Physical symptoms	2.41 (1.2)	1.67 (0.8)	2.15 (0.9)	3.28 (1.1)	2.45 (1.3)	.000
Retrospective at debriefing						
EQ-5D VAS	74.37 (19.6)	90.50 (8.8)	56.93 (19.2)	72.75 (17.5)	70.73 (17.4)	.000

SD=standard deviation; VAS=visual analogue scale; HRQOL= health-related quality of life measured with a VAS;
* One-way ANOVA on retrospective and aggregated momentary data

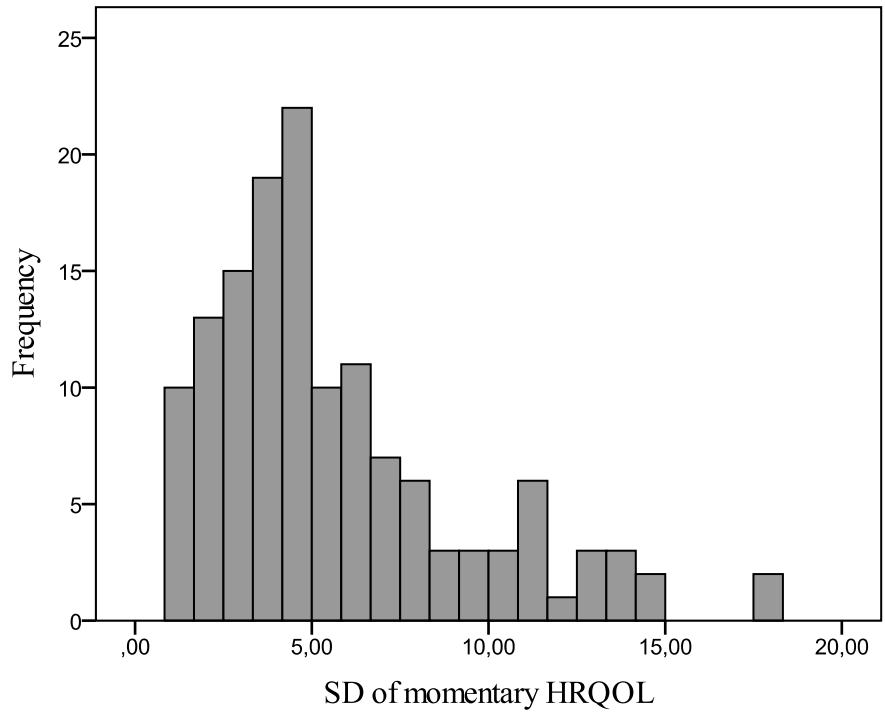


Figure 1. Frequency of within person SD's of momentary HRQOL

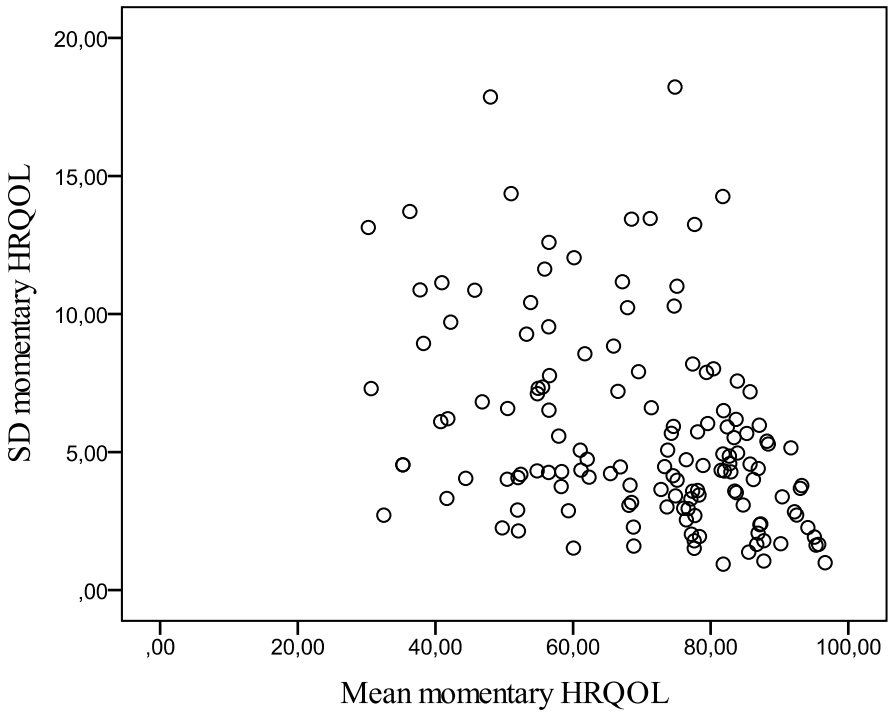


Figure 2. Relation between mean momentary HRQOL and SD of momentary HRQOL per subject.

Relation between momentary experienced feelings and symptoms and momentary valuation of HRQOL

The aggregated means of PA, NA and PS are displayed in Table 2. Six participants showed no variance in PA, NA or PS, so data for these participants are not included in the following analyses. The mean correlation between momentary HRQOL and PA, NA and PS were respectively 0.35 (range -0.28 to 0.91), -0.22 (range -0.86 to 0.30) and -0.26 (range -0.90 to 0.30). The within person correlations between the HRQOL and feelings (PA and NA) and physical symptoms (PS) for the total sample are displayed in Figure 3. In 86% of the total sample the relation between momentary HRQOL and PA was positive. In 37% of the patients with a positive relation between momentary HRQOL and PA this correlation was high (>.50). The highest proportion of patients with a negative correlation between the HRQOL and PA was in the somatic complaints sample (22%). The difference between the samples in the proportion of patients with a positive or negative correlation between momentary HRQOL and PA was not statistically significant (χ^2=4.2; p=0.240). In 75% of all participants the relation between momentary HRQOL and NA was negative and in 17% of all participants this correlation was high. The highest proportion of participants with a positive correlation between momentary HRQOL and NA was again in the somatic complaints sample (47%). The difference between the samples in the proportion of participants with a positive or negative correlation between momentary HRQOL and and NA was statistically significant (χ^2=15.5; p=0.001). In 81% of the participants the relation between momentary HRQOL and PS was negative and in 19% this was a high correlation (>.50). In 25% of the tinnitus sample and the somatic complaints sample a positive correlation between momentary HRQOL and PS was found. There was no significant difference between the different samples regarding the proportion of participants with a positive or negative relation between momentary HRQOL and PS (χ^2=6.2; p=0.101). In Table 3 the results of the multilevel analysis are

displayed. The results of the final model showed that all variable estimates were in the expected direction. At the .05 level a significant main effect for PA and PS was found when controlling for age, sex and sample. A significant for NA was found at the .10 level. PA had significant interaction effects with psychological complaints and tinnitus sample. This means that PA is a stronger predictor of momentary HRQOL among those with psychological and tinnitus complaints, than other complaints. Although the main effect of NA was not significant at the .05 level, NA had a significant interaction with psychological complaints sample. This means that NA is a stronger predictor of momentary HRQOL in this sample compared to other samples. With regard to PS, a significant interaction was found with the psychological complaints sample and the tinnitus sample. This implies that PS is a stronger predictor of HRQOL in these samples than in the other samples.

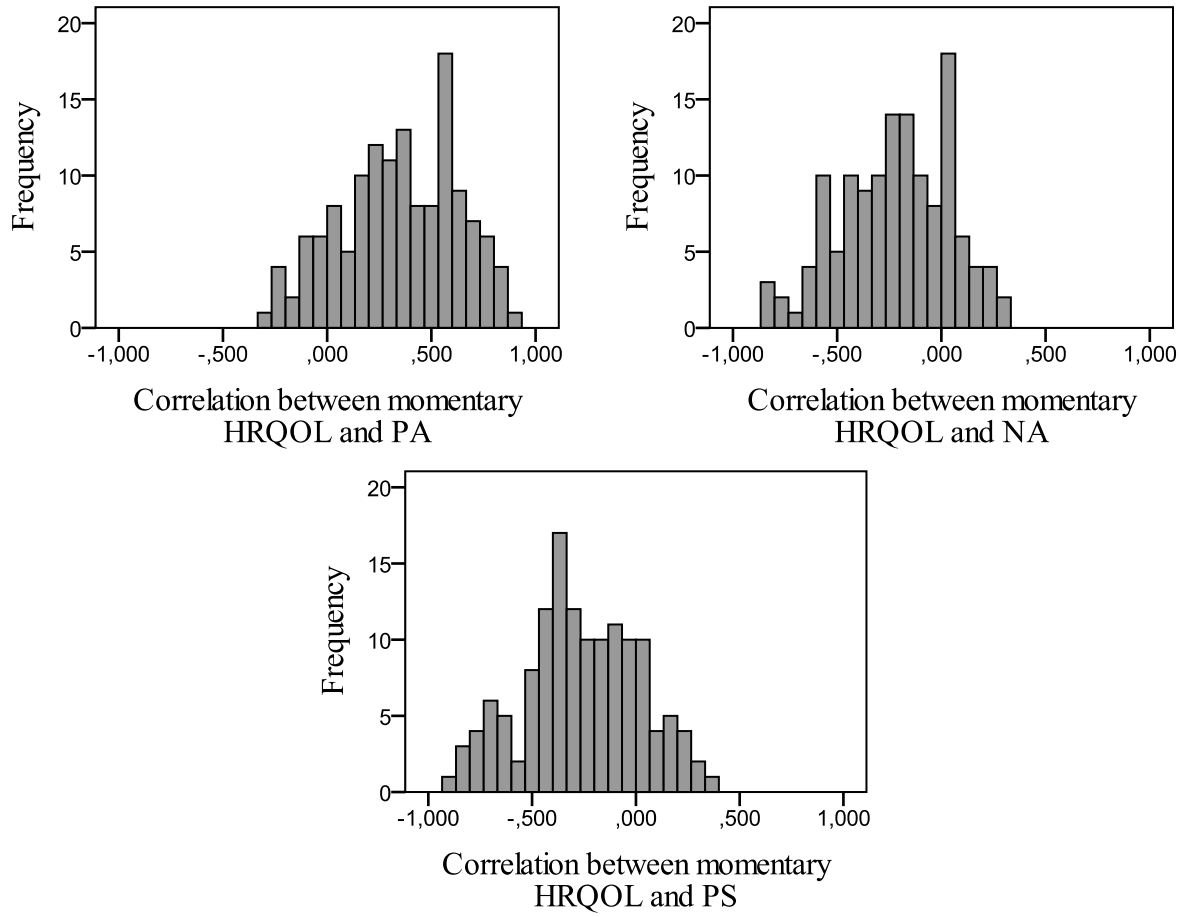


Figure 3. Frequencies of within person correlations between mom-HRQOL and PA, NA and PC.

Table 3. Variance in momentary valuation of HRQOL explained by positive affect (model 3), negative affect (model 4) and physical symptoms (model 5) and their interaction with group represented in three dummy variables (model 6).

	Model 1 (intercept only)			Model 2			Model 3		
N=5977	β	SE	P-value	β	SE	P-value			
Intercept	-0.018	0.081	.824	0.672	0.155	.000	0.542	0.122	0.000
Dummy 1 (Psychological)				-1.353	0.206	.000	-0.927	0.162	0.000
Dummy 2 (Tinnitus)				-1.160	0.224	.000	-0.934	0.177	0.000
Dummy 3 (Somatic)				-1.148	0.249	.000	-0.940	0.196	0.000
Age				0.364	0.148	.014	0.113	0.076	0.134
Sex				0.154	0.096	.110	0.244	0.117	0.037
Positive affect							0.356	0.010	0.000
Variance	Random			Random			Random		
Person level	0.951			0.818			0.643		
Beep level	0.375			0.375			0.340		
Model fit	-3006.19			-2990.59			-2392.94		
Explained variance									
Person level				14%			21%		
Beep level				0%			9%		

	Model 4			Model 5			Model 6		
N=5977	β	SE	P-value	β	SE	P-value			
Intercept	0.564	0.136	.000	0.481	0.127	.000	0.488	0.109	.000
Dummy 1 (Psychological)	-1.109	0.181	.000	-1.197	0.168	.000	-0.870	0.146	.000
Dummy 2 (Tinnitus)	-1.043	0.197	.000	-0.617	0.184	.001	-0.634	0.159	.000
Dummy 3 (Somatic)	-1.041	0.218	.000	-0.847	0.203	.000	-0.828	0.175	.000
Age	0.110	0.084	.192	0.234	0.121	.121	0.210	0.067	.244
Sex	0.377	0.130	.004	0.121	0.078	.053	0.079	0.104	.043
Positive affect							0.176	0.020	.000

Negative affect	-.0223	0.009	.000				-0.040	0.022	.071
Physical symptoms				-0.355	0.011	.000	-0.159	0.025	.000
Dummy 1 * positive affect							0.161	0.161	.000
Dummy 2 * positive affect							0.136	0.136	.000
Dummy 3 * positive affect							0.033	0.033	.280
Dummy 1 * negative affect							-0.057	-0.057	.036
Dummy 2 * negative affect							-0.046	-0.046	.119
Dummy 3 * negative affect							0.023	0.023	.458
Dummy 1 * physical symptoms							-0.091	-0.091	.008
Dummy 2 * physical symptoms							-0.134	-0.134	.000
Dummy 3 * physical symptoms							0.015	0.015	.676
Variance									
Person level	0.716			0.666			0.573		
Beep level	0.359			0.350			0.322		
Model fit	-1273.48			-2557.27			-2093.17		
Explained variance									
Person level	12%			19%			30%		
Beep level	4%			7%			14%		

SE=Standard Error

Dummy 1: 1=Psychological complaint sample, 0=Tinnitus sample, 0=Somatic complaints sample. Dummy 2: 1=Tinnitus sample, 0= Psychological complaint sample, 0=Somatic complaints sample. Dummy 3: 1=Somatic complaints sample, 0=Tinnitus sample, 0=Psychological complaint sample. Reference group = general population sample.

Table 4. Correlations between momentary outcomes and the EQ-5D VAS

Group	Momentary outcomes ESM	Global retrospective outcome EQ VAS Briefing	EQ-VAS Debriefing
	Health-related quality of life		
Total sample		*0.810*	*0.826*
General population sample		0.56	0.62
Tinnitus sample		0.86	0.88
Psychological complaints		0.80	0.85
Somatic complaints		0.69	0.65
	Positive affect		
Total sample		*0.630*	*0.686*
General population sample		0.52	0.48
Tinnitus		0.62	0.68
Psychological complaints		0.58	0.64
Somatic complaints		0.69	0.65
	Negative affect		
Total sample		*-0.562*	*-0.628*
General population sample		-0.28	-0.21
Tinnitus		-0.60	-0.59
Psychological complaints		-0.55	-0.68
Somatic complaints		-0.40	-0.50
	Physical complaints		
Total sample		*-0.489*	*-0.519*
General population sample		-0.32	-0.36
Tinnitus		-0.62	-0.68
Psychological complaints		-0.14	-0.47
Somatic complaints		-0.53	-0.68

VAS = visual analogue scale

Relation between momentary HRQOL, feelings and symptoms and global retrospective HRQOL.

Table 2 gives an overview of the mean and SD's for the aggregated momentary HRQOL, PA, NA and PS and the EQ VAS at briefing and debriefing, for the total sample. There was a significant difference between mean momentary HRQOL (70.16) and mean EQ VAS (72.85) at briefing (paired samples t-test; t=-3.111; p=.002), but not between mean momentary HRQOL and mean EQ VAS (74.37) at debriefing (paired samples t-test; t=1.010; p=.314). Table 5 displays the correlations between momentary ESM data and the EQ VAS for the total sample and the different sub-samples. The correlation between PS and EQ VAS at briefing was low in the psychological complaints group. The correlations between mean NA and the EQ VAS were low for the population based sample. When EQ VAS at debriefing was predicted by momentary experiences (and corrected for group differences, age, sex and EQ VAS at briefing) without taking into account the interaction effects between momentary experiences and sample, it was found that only PS ($\alpha<.05$) and NA ($\alpha<.10$) were significant predictors of EQ VAS (Table 5). If the interaction terms were added to the model, only the relationship between NA and EQ VAS in the somatic complaints group was significant (Table 5). This means that NA is a stronger predictor of EQ VAS among persons with somatic complaints than in the other samples.

Table 5. Variance in EQ VAS explained by positive affect, negative affect and physical symptoms (model 1) and their interaction with group represented in three dummy variables (model 2).

	Model 1		Model 2	
N=139	β	P-value	β	P-value
Dummy 1 (Psychological)	-0.023	.839	-0.086	.514
Dummy 2 (Tinnitus)	0.216	.130	-0.051	.750
Dummy 3 (Somatic)	-0.156	.245	-0.381	.007
Age	-0.072	.522	-0.014	.898
Sex	-0.128	.162	-0.090	.315
EQ VAS	-0.092	.520	-0.193	.191
Positive affect	-0.088	.561	0.111	.785
Negative affect	-0.247	.076	0.099	.832
Physical symptoms	-0.359	.008	0.212	.691
Momentary HRQOL	-0.041	.823	0.302	.521
Dummy 1 * Positive affect			-0.045	.863
Dummy 2 * Positive affect			-0.090	.731
Dummy 3 * Positive affect			-0.220	.328
Dummy 1 * Negative affect			-0.038	.903
Dummy 2 * Negative affect			-0.086	.770
Dummy 3 * Negative affect			-0.552	.013
Dummy 1 * Physical symptoms			-0.080	.691
Dummy 2 * Physical symptoms			-0.099	.774
Dummy 3 * Physical symptoms			-0.376	.201
Dummy 1 * Momentary HRQOL			0.001	.996
Dummy 2 * Momentary HRQOL			0.025	.928
Dummy 3 * Momentary HRQOL			-0.217	0.327
Explained variance				
R^2	0.197		0.370	
Adjusted R^2	0.134		0.269	

HRQOL=health-related quality of life
Dummy 1: 1=Psychological complaint sample, 0=Tinnitus sample, 0=Somatic complaints sample. Dummy 2: 1=Tinnitus sample, 0= Psychological complaint sample, 0=Somatic complaints sample. Dummy 3: 1=Somatic complaints sample, 0=Tinnitus sample, 0=Psychological complaint sample. Reference group = general population sample.

Discussion

This article reports on what is, to our knowledge, the first study that uses the ESM to obtain accounts of the momentary experience of HRQOL and compare these with measures used to calculate QALYs. The results for each research question will be discussed in the next paragraphs.

In answering the first research question regarding the feasibility of using the ESM approach to obtain accounts of momentary experience of HRQOL, two things need to be considered: the overall participation rate and the response rate in the persons that agreed to participate. The overall participation rate was low in the patient groups, especially in the tinnitus population and the atherosclerosis/venous insufficiency group. The most common reason for not wanting to participate was that people were not interested in the study objective, which was measuring quality of life in daily life instead of retrospectively and thus not a particular problem for the

methodology. It was an observational study and therefore not part of any treatment that could be of interest to the patients. More research has to be done to learn more about the feasibility of using the ESM to obtain accounts of the momentary experience of HRQOL as part of a randomized controlled trial. Another common reason for not participating was 'too burdensome', which is related to the method. The low participation rate in the tinnitus population was probably a result of the fact they had just completed a 12-month RCT in which they had to answer a substantial amount of questionnaires. For the atherosclerosis/venous insufficiency group the higher mean age of the group could be an explanation for the low participation rate. Although it was clearly stated in the information letter that the PsyMate is a user-friendly device, a lack of experience with these electronic devices (Olson et al., 2011) could deter older participants. Furthermore, part of the group that was approached just underwent an intensive (clinical) rehabilitation programme because of a leg amputation. With regard to the response rate to the data collected during the study all participants that finished the briefing also finished the ESM week and the debriefing (with the exception of only 1 participant). The participants on average answered to 72% of the beeps, which is comparable to other studies (Knouse et al., 2008; Roelofs et al., 2004; Thewissen et al., 2008). The fact that beeps are missing is not problematic for the statistical analysis, since the major advantages of the ESM is that it collects several data points for each respondent. Therefore the respondent can miss about two third of the beeps without being excluded from the analyses. Furthermore the majority of the participants reported the week was representative of a typical week in and that the PsyMate did not influence their health or mood. In this respect, feasibility is more than satisfactory. We can conclude that the low participation rate in this study might be the result of a motivational problem related to not knowing what to expect from the ESM.

With regard to the second research question we can conclude that there is some variability from moment to moment in momentary HRQOL. This indicates that people take different things into consideration when making a momentary assessment of their HRQOL during the day. A significant within-person relation between mean momentary experienced HRQOL and the variability from moment to moment was found: the lower mean momentary HRQOL, the more variability during the ESM week. This could be a result of a ceiling effect on momentary HRQOL. To explore whether this was the case, we computed the SD for participants with a ceiling effect on momentary HRQOL (>90), and the correlations between mean and SD. The results show that the SD was 1.1, and the correlations were equal in the four groups (tested with a fisher z-transformation; $\chi 2=6.93$). These findings suggest that a ceiling effect only has a limited effect on the data. Moreover, the findings are in line with other research that found more variability in patients with worse mood levels (higher on NA and lower on PA) (Hedeker et al., 2012). With regard to this research question, there is at least one possible drawback of the study. Momentary assessment of experienced HRQOL was one of the last questions in the beep questionnaire. The reason for this is that feelings can be influenced by preceding questions and therefore have to be measured first after the beep. Because of this it could be that the variability found in momentary experienced HRQOL is the result of a framing effect. Further research should focus on the question whether the variability found in momentary experienced HRQOL reflects real differences in experienced health. Also order effects of the different questions in the ESM could be investigated.

The third research question focused on the relation between momentary HRQOL and feelings and symptoms during the same period. The analyses showed that PA, PS ($\alpha<.05$) and NA ($\alpha<.10$) are significant predictors of momentary HRQOL. This means that momentary specific feelings and symptoms predict the momentary valuation of HRQOL. In addition it was found

that these relations are stronger among those with psychological complaints (PA, PS and NA) and tinnitus (PA and PS), than among persons with somatic complaints and the population based sample. This may imply that persons who experience psychological complaints and tinnitus rely more on the momentary experience of feelings and symptoms, when valuing their global momentary HRQOL than persons in the other samples. Recent literature has stressed the conceptual differences between momentary and global assessment (Tay et al., in press). Momentary reports reflect current affective or physical states, whereas global assessment is based upon some self-reflection processes like introspection and self-observation. In other words, global assessments of HRQOL rely more on general beliefs, whereas momentary reports rely on experience (Schwarz et al., 2009). Perhaps, in the psychological complaints and tinnitus sample a global concept like momentary HRQOL is influenced more by experience, while in persons with somatic complaints and the population based sample the momentary valuation of HRQOL may be more linked to general beliefs. Further research should focus on whether groups differ with regard to specific valuation strategies used to value momentary HRQOL, for instance by using a follow-up question directly after the valuation task.

In the fourth research question the relations between a retrospective global measure of HRQOL (EQ VAS) and the moment-to-moment valuation of HRQOL, and experience of feelings and symptoms, were examined. High correlations were found between the EQ VAS and momentary HRQOL. This finding was expected since the framing of the questions was similar in both methods. The multiple regression model that was fitted to the data revealed that if the interaction terms were added to model, none of the momentary feelings and symptoms were significant predictors of EQ VAS. Also, momentary experienced HRQOL was not a significant predictor of EQ VAS. This supports earlier findings that global reports of past health will rely more on beliefs (semantic memory) than on specific feelings and symptoms (Kahneman et al., 2004; Robinson & Clore, 2002; Stone et al., 2006). However, NA was a stronger predictor of EQ VAS among persons with somatic complaints than in the other samples. This may suggest that somatic complaints are more associated with a retrospective global valuation of HRQOL, such as EQ VAS, than psychological and tinnitus complaints. Perhaps somatic complaints are more related to semantic memory and psychological and tinnitus complaints are more related to episodic memory. This highlights the problem that global measures do not reflect the actual impact of health problems, particularly in populations with psychological or tinnitus complaints. More research is necessary to examine this finding.

In this paper we only focused on momentary HRQOL and feelings and symptoms. However, ESM data also hold information on contextual items that could look more in detail at the different dimensions of health in the retrospective questionnaires. For instance, is the mobility dimension as measured by the EQ-5D reflected by the different locations a person is at during the day as measured by the ESM. These questions are beyond the scope of this paper, but need to be considered in future papers. Although this paper focuses on the patient perspective, the ESM could also have added value when a societal perspective is adopted. From a societal perspective health state values need to be obtained in the general public. The ESM could be useful in describing a health state since it may be more able to capture what is important to a patient in terms of health and HRQOL than a retrospective descriptive system like the EQ-5D. Future research should focus on how the ESM data can be used to inform members of the general public on different health states so the valuation of a health state may become more accurate.

We can conclude that the use of the ESM to measure accounts of the momentary experience of health in different populations is feasible. The results showed that within persons the valuation of global HRQOL and specific feelings and symptoms are variable from moment to moment. Also, the relation between momentary specific feelings and symptoms and the momentary valuation of HRQOL differed among populations. A global retrospective valuation of HRQOL was not predicted by momentary feelings, symptoms and HRQOL. This highlights that retrospective measures may provide a biased account of the impact of health problems in the daily lives of people who are affected. Moreover, the bias may be different in different conditions.

APPENDIX A

I am feeling							
	Not			Moderate			Very
1. Cheerful	1	2	3	4	5	6	7
2. Insecure	1	2	3	4	5	6	7
3. Relaxed	1	2	3	4	5	6	7
4. Anxious	1	2	3	4	5	6	7
5. Enthusiastic	1	2	3	4	5	6	7
6. Satisfied	1	2	3	4	5	6	7
7. Sad	1	2	3	4	5	6	7
8. Happy	1	2	3	4	5	6	7
9. Tired	1	2	3	4	5	6	7
10. Sick	1	2	3	4	5	6	7
I am/have							
	Not			Moderate			Very
11. Hungry	1	2	3	4	5	6	7
12. Pain	1	2	3	4	5	6	7
13. Tinnitus	1	2	3	4	5	6	7
14. Overall I am feeling good	1	2	3	4	5	6	7

15. **What am I doing (right before the beep)?**
Answering categories: Relaxing/Active; Relaxing Passive; Nothing; Work/Study; Household; Talking; Self-care; Care for others; Medical care; Eating/Drinking; In transit; Other

16. **Where am I?**
Answering categories: at home; at work; at someone else's home; public place; healthcare setting; outside; other

17. **Who am I with** (including telephone contacts, chatting etc.)?
Answering categories: partner; people living at home; family living somewhere else; friends; colleagues; acquaintances; unknown others; nobody (3 possibilities)

18. Number of people you are with? (Answering categories: 1-6 />6)

	Not			Moderate			Very
19. This company is pleasant	1	2	3	4	5	6	7
20. I would rather be alone	1	2	3	4	5	6	7
21. We are doing something together	1	2	3	4	5	6	7
When alone:							
22. I like being alone	1	2	3	4	5	6	7
23. I would rather be in company	1	2	3	4	5	6	7

24. **My health state right now is:**
(Please mark an X on the line that shows how good or bad your health is at this moment):

Think about the most important event that happened since the last beep.
This was:

25. Very unpleasant	-3	-2	-1	0	1	2	3	Very pleasant
26. Very unimportant	-3	-2	-1	0	1	2	3	Very important

27. This event was something**:**
That happened to me; something I had an influence on; Something regular / routine; a feeling or thought; other

29. This was the result of:
Contact with others; The surroundings; own condition; activity; new information; other

30. This beep disturbed me: Yes No

CHAPTER 6

The effects of tinnitus on daily life: an experience sampling study

Iris H.L Maes, Madelon L. Peters, Philippe A.E.G. Delespaul,
Lucien J.C. Anteunis, Manuela A. Joore

Submitted for publication

Abstract

Objectives The aim of this study is to explore whether emotions, activities and social interactions in daily life of patients with tinnitus are different from a population based sample. Furthermore, the association between effects of tinnitus severity and the level of positive affect, negative affect, physical complaints, activity and social interactions in daily life is examined.

Methods Forty patients with tinnitus and forty persons from a population based sample were studied with the Experience Sampling Method (ESM). ESM is a structured diary technique in which participants are prompted with a beep (and vibrations) to complete assessments of their current emotions, physical complaints and contextual items at random times during the day.

Results Multilevel regression analysis confirmed a significant difference between the samples with regard to positive affect, negative affect and physical symptoms, but not with regard to activities or social interactions. When tinnitus intensity is experienced as more severe, there is a concomitant increase in pain and fatigue. In addition, more severe tinnitus is accompanied by more negative and less positive mood.

Conclusion Tinnitus has a major impact on daily life. Patients suffering from tinnitus experience more emotional and physical complaints than a population based sample, and with increasing tinnitus severity there is a worsening of these complaints.

Keywords Tinnitus, Experience Sampling Method, Negative affect, Positive affect, Physical symptoms

Funding Funding was received from the Netherlands Organization for Health Research and Development (project number 80-82500-98-9207).

Introduction

Tinnitus is often described as an auditory phantom sound, a sound in the ear or in the head without the presence of an external source. The prevalence of tinnitus in the western world is estimated between 10-20% (Andersson, 2002; Davis & El Refaie, 2000) and approximately 3-5% of the general population is severely impaired by the tinnitus (Davis & El Refaie, 2000; Vesterager, 1997).Patients often report cognitive impairments (problems with attention and concentration) and negative emotions (anxiety and depressive symptoms) (El Refaie et al., 2004; Hallam et al., 2004). In most cases tinnitus is a subjective experience for which there is no detectable organic cause. But some somatic conditions can cause objective tinnitus (e.g. a vestibular schwannoma, cholesteotoma or temporal bone trauma (Newman et al., 2011)). It is important to rule out these conditions as they can be life threatening and treatment may eliminate the tinnitus. Tinnitus without a known organic cause cannot be eliminated. In this situation most treatments focus on eliminating the subject's reactions induced by the tinnitus (Henry et al., 2005; Jastreboff & Jastreboff, 2006; Martinez-Devesa et al., 2010). Some treatments are based on Jastreboff's neurophysiological model of tinnitus, an integral heuristic (Jastreboff et al., 1996). In this model emotional reactions such as anxiety, depression and cognitive problems as concentration, are the result of an inappropriate activation of the limbic and sympathetic part of the autonomic nervous system (Jastreboff et al., 1996; Jastreboff & Jastreboff, 2006; Zenner & Zalaman, 2004). Other treatments are based on cognitive behavioral therapy. They assume that faulty thought patterns (cognitions) about the tinnitus cause maladaptive behavior and emotional responses that maintain or contribute to tinnitus-related problems (Cima et al., 2012; El Refaie et al., 2004; Gudex et al., 2009; Hesser et al., 2011; Martinez-Devesa et al., 2010).

Several studies have confirmed that tinnitus annoyance correlates closely with a patients degree of anxiety, depression and sleep disturbance (Erlandsson et al., 1991; Folmer et al., 2001; Langenbach, 2005; Zoger et al., 2006). Anxiety and depression scores were elevated in tinnitus patients, compared to healthy controls or non-help seeking tinnitus sufferers (Attias et al., 1995; Scott & Lindberg, 2000). Also, patients with tinnitus display increased somatic attention and somatisation (Hiller et al., 1994; Hiller et al., 1997; Newman et al., 1997). They often experience social withdrawal and seem reluctant to participate in "normal" interpersonal contacts of day-to-day life (Davis & El Refaie, 2000; Folmer et al., 1999; Hiller & Haerkotter, 2005; Newman et al., 2011). Interference with other daily activities such as self-care activities, occupational activities and leisure time activities has been demonstrated as well (Cima et al., 2011).

Most studies on the influence of tinnitus on daily life were conducted using self-report questionnaires. These rely on retrospective assessment of past experiences. Several studies have shown that recalled information is prone to bias (see Robinson & Clore, 2002). The Experience Sampling Method (ESM) was designed to reduce the influence of biases due to less than perfect recollection. It contains a measure of hedonic and affective experience derived from immediate reports of current subjective experience. Moreover, ESM enables to not only assess associations between the tinnitus experience and emotional and physical complaints across individuals, but also within a single individual. This yields information regarding the question whether fluctuations in tinnitus severity are related to emotional, social and behavioral interference. Furthermore time-lag analyses can be used to determine the prospective and bi-directional relation between symptoms of tinnitus and emotional, social and behavioral precursors or consequences.

The ESM has some potential limitations. It can be time consuming and potentially burdensome to participants and therefore it is important to minimize the length of the questionnaires. Furthermore, ESM could evoke 'reactivity', which means that the experience

being measured is changed by the fact that it is measured. Reactivity can be minimized by framing questions as neutral as possible (Conner et al., 2009).
The objective of this study is to explore differences in emotions, activities and social interactions in daily life of patients with tinnitus and a population based sample. It was expected that patients with tinnitus report higher levels of negative affect and lower levels of positive affect. Also, it was expected that patients with tinnitus report more physical complaints, experience more social withdrawal and are less active than a population based sample. Within patients with tinnitus the association between effects of tinnitus intensity and the level of positive affect, negative affect, physical complaints, activity and social interactions in daily life is examined. It is expected that there is a significant relation between the intensity of tinnitus and positive affect, negative affect, physical complaints, activity level and social interactions. Time-lag analysis will be used to determine whether tinnitus intensity at one moment predicts positive affect, negative affect, physical complaints, activity level and social interactions at the next moment and/or whether increases in positive affect, negative affect, physical complaints, activity level and social interactions precede increases in tinnitus intensity.

Methods

Participants

Forty patients with tinnitus and a population based sample of 40 persons were included in this study. The patients with tinnitus were recruited from a completed randomized controlled trial investigating a multidisciplinary treatment for tinnitus versus care as usual (Cima et al., 2009; Cima et al., 2012). Inclusion criteria were (a) referral to an audiological centre because of tinnitus complaints, and (b) being 18 years or older. Exclusion criteria were (a) an organic cause of tinnitus, (b) not able to read in Dutch, and (c) not able to handle the ESM device because of impaired motor skills. Of the 325 patients that received the study information, 45 were willing to participate in this study and returned a written informed consent. Of these 45 patients, four did not come to the briefing or cancelled their participation before the briefing. One patient was not able to read the text on the ESM device because the font size was too small. The population based sample was recruited through advertisements/posters in the Maastricht University Hospital. Forty-four persons responded to this poster and received the study information. Forty participants returned the written informed consent. All 80 participants that finished the briefing, completed the ESM week. Participants received €25 remuneration for their full participation. The Ethics Committee of the Maastricht University Hospital approved the study protocol.

Measures

Experience Sampling Method

ESM studies are usually performed with a digitized wrist watch or pager and a pocket sized question booklet, PDA's or smart phones. In this study we used the PsyMate (www.psymate.eu), a small user-friendly device programmed to generate beeps (and vibrations) at unpredictable moments of the day between 7.30h and 22.30h over 6 consecutive days. Subjects use a touch screen to fill out the questions and response-logs were time- and date-stamped. Data captured from the PsyMate were transferred to a PC where software turned data into STATA data files.
Current tinnitus intensity was assessed with the item 'Right now, I experience tinnitus', rated on 7-point Likert scales from 1='not at all' to 7='very much'. Other current physical symptoms were assessed using ratings on pain, tiredness and feeling sick. Current positive affect was assessed using ratings on the items cheerful, relaxed, enthusiastic, satisfied, energetic and happy. Current negative affect was assessed by means of the items insecure,

anxious, lonely, down, and irritated. All items were rated on the same 7-point Likert scale. Positive and negative affect were determined by calculating the mean of the relevant items. For assessing their current actual activity, participants could choose from 10 different descriptive categories or the category "other" in case none of the categories was suitable (see Figure 1). Current perceived activity level was measured with the item 'I find myself active' also on the same 7-point Likert scale. Current social interactions were assessed by choosing from 8 different descriptive categories (see Figure 2).

Retrospective measures
The Hospital Anxiety and Depression Scale (HADS) was administered in the total sample to measure severity of anxiety and depressive complaints (Spinhoven et al., 1997). Tinnitus burden and severity was assessed in the patient group with the Tinnitus Questionnaire (TQ). The Dutch validated TQ (Meeus et al., 2007) was administered during the follow-up of the RCT from which the patients of the present study were recruited. At the beginning of this RCT a mean pure tone threshold at 1, 2 and 4 kilohertz was determined.

Procedure

Before the start of the ESM week participants were carefully instructed during an individual briefing session. The rationale of the study was explained and subjects were instructed how to use the PsyMate. Anticipated problems were discussed and the questionnaires on the device were reviewed during a simulated try-out sampling moment.

Data analysis

A multilevel (or hierarchical) regression analysis is ideally suited for data obtained with the ESM since beep level data (level 1) are nested within persons (level 2). In multilevel analysis a curve is fitted for the dependent variable for each participant, thereby taking into account the fact that beep-level measures of within patients measures tend to be more alike than randomly chosen beep level measurement. The odds ratio (for dichotomous variables) and B's (for continuous variables) reflect the association between the independent and dependent variables in the multilevel model. All analyses involving the ESM data were therefore computed with the XTMIXED (for continuous variables) and XTMELOGIT (for dichotomous variables) modules of STATA 11.0.
To explore whether patients with tinnitus differed from the population based sample in overall symptom level, multilevel regression analyses were conducted using group (0=population based sample, 1=tinnitus sample) as the independent variable, and using negative and positive affect items and physical complaint items as dependent variables in consecutive models. To examine whether there were differences between patients and the population based sample, perceived activity level, actual activity level (dichotomized as: 0=doing nothing or passive relaxing; 1= any other activity) and social interactions (0=alone; 1=not alone) were assessed as dependent variables in the multilevel regression analyses and group as independent variable. Since differences between the samples in age, sex, hearing loss (as measured by having a hearing aid or not) and having a paid job could influence the relations under investigation, all analyses were corrected for these variables.

To examine whether tinnitus intensity was associated with positive affect, negative affect, physical symptoms, perceived activity level, actual activity level and social interactions in patients with tinnitus, a multilevel random regression model was estimated with tinnitus intensity as the dependent variable and the other variables as independent variables. To correct for hearing loss, the mean pure tone threshold at 1, 2 and 4 kilohertz was included in the analysis as a covariate. A stepwise procedure was used to add variables to the model. If

there was a significant change in the model, the variable was included in the model. If there was no significant change the variable was excluded. Each model change was tested for significance using a likelihood ratio test with 'k' degrees of freedom (k=the difference in number of parameters between 2 successive models).

To determine the extent to which positive affect, negative affect, physical symptoms, activity level and social interactions at one moment (t-1) predicted tinnitus at the next moment (t), between 20 and 120 minutes later on the same day, a time-lag function was determined for all the relevant variables. The first beep of each day was removed from the data, to minimize the interval between two subsequent beeps. If one beep was not responded to, then the consequent data in the next beep was removed from the analysis. As a result 445 beep measurements were removed from the analysis. A model was fitted to the remaining data (N=1310) with tinnitus as the dependent variable. Both positive affect, negative affect, physical symptoms, activity level and social interactions (t), as their time-lagged variants (t-1) were included into the model following a stepwise procedure. Since it is expected that tinnitus intensity at one moment also has an effect on tinnitus intensity at the next moment, the analysis were corrected for this so called autoregressive effect. A time-lag function for tinnitus intensity (t-1) was therefore included in the analysis as a covariate. The analysis were also corrected for hearing loss by including the mean pure tone threshold at 1, 2 and 4 kilohertz as a covariate. Each model change was tested for significance using a likelihood ratio test with 'k' degrees of freedom (k=the difference in number of parameters between 2 successive models).
To examine if tinnitus intensity at one moment (t-1) predicted positive affect, negative affect, pain, tiredness, feeling sick, (actual and perceived) activity level and social interactions at the following moment (t) (dependent variables). Separate linear multilevel models were estimated with positive affect, negative affect, several physical symptoms, activity level or social interactions as the dependent variable and tinnitus intensity at t and t-1 as independent variables. These models were corrected for an autoregressive effect of the dependent variables by including a time-lag function of these variables into the analysis. The independent variables were included in the models following a stepwise procedure. Each model change was tested for significance using a likelihood ratio test with 'k' degrees of freedom (k=the difference in number of parameters between two successive models).

Results

With regard to the tinnitus sample, differences between the group of patients that received the study information and those that were willing to participate are displayed in Table 1. There were no significant differences with regard to age, sex and education, but the TQ score was significantly higher in the patients that were willing to participate. Demographic characteristics of the tinnitus and the population based sample are summarized in Table 2. There were significant differences between the patients with tinnitus and the population based sample with regard to all demographic variables. In addition, the score on the HADS was significantly higher in the tinnitus sample. Patients with tinnitus on average responded to 42 beeps, with a minimum of 25 and a maximum of 55. The participants in the population based sample on average responded to 44 beeps, with a minimum of 17 and maximum of 59. In total 71.3% of the beeps were completed; 69.5% in the population based sample and 73.2% in the tinnitus population.
Overall, patients with tinnitus reported significantly lower levels of positive affect and higher levels of negative affect than participants from the population based sample (Table 3). Positive affect items that were significantly different between both groups were feeling cheerful (B=-0.89, P=0.02), relaxed (B=-1.07, P=0.00), satisfied (B=-1.00; P=0.00) and energetic (B=-0.98; P=0.025). Negative affect items that were significantly different between

Table 1. Demographic characteristics of patients with tinnitus who were willing to participate and patients with tinnitus who were not willing to participate in this study based on data collected during a completed randomized controlled trial

Characteristics	Included in this study	Not willing to participate / drop-out	P-value*
N	40	285	
Age (SD)	56.0 (11.4)	54.0 (11.9)	.291
Sex (% male)	29 (72.5)	171 (60.0)	.128
Mean PTT at 1, 2 & 4 kHz (in decibel)	34.6 (19.7)	31.1 (18.0)	.309
Education (%)			.570
Low	14 (35.0)	82 (28.8)	
Middle	14 (35.0)	124 (43.5)	
High	12 (30.0)	79 (27.7)	
Available data at end of trial			
N (% missing data)	35 (12.5)	196 (31.2)	
TQ score (SD)	46.2 (20.5)	37.4 (19.4)	.023

* Independent samples t-test for continuous variables and χ^2 for categorical variables
SD=Standard Deviation ; TQ=Tinnitus Questionnair; PTT=Pure Tone Treshold; kHz=kilohertz

Table 2. Demographic characteristics of the participants in this study

Characteristics	Population based sample	Tinnitus sample	P-value*
N	40	40	
Age (SD)	38.6 (14.6)	58.2 (10.0)	.000
Sex (% male)	11 (27.5)	29 (72.5)	.000
Paid job / student (% yes)	38 (95.0)	23 (57.5)	.000
Living situation (% alone)	13 (32.5)	4 (10.0)	.014
Education (%)			.002
Low	4 (10.0)	14 (35.0)	
Middle	9 (22.5)	14 (35.0)	
High	27 (67.5)	12 (30.0)	
HADS score	12.1 (4.0)	16.9 (6.7)	.000
Hearing aid (% yes)	1 (2.5)	20 (50.0)	.000

SD = Standard Deviation; HADS = Hospital Anxiety and Depression Scale
* Independent samples t-test for continuous variables and χ^2 for categorical variables

groups were feeling insecure (B=0.98; P=0.03) and anxious (B=0.71; P=0.07). With regard to physical complaints, patients with tinnitus reported, as expected, significantly more tinnitus but also more pain than participants from the population based sample (Table 3). They also reported being more tired and sick (Table 3).

Figure 1 shows that there was a significant difference between the groups in the type of activity they were involved in (χ^2=168; p<.000). Participants from the population based sample more often indicated to be working/studying at the time of the beep compared to tinnitus patients, while patients with tinnitus more often indicated to be doing nothing (standardized residuals>1.96). However, there were no significant differences in the perceived

activity level and the dichotomized actual activity level between the two groups. The difference in actual activity level was mostly predicted by having a job or not (Odds ratio=1.526). There was no difference between patients with tinnitus and the population based sample in the number of beeps spent alone or in the company of another person. Figure 2 displays that there is a difference between the groups in the type of relationship with the persons with whom participants interacted (χ^2=274; p<.000). Patients more often indicated to be with their partner and less with colleagues, residents and strangers (standardized residuals>1.96).

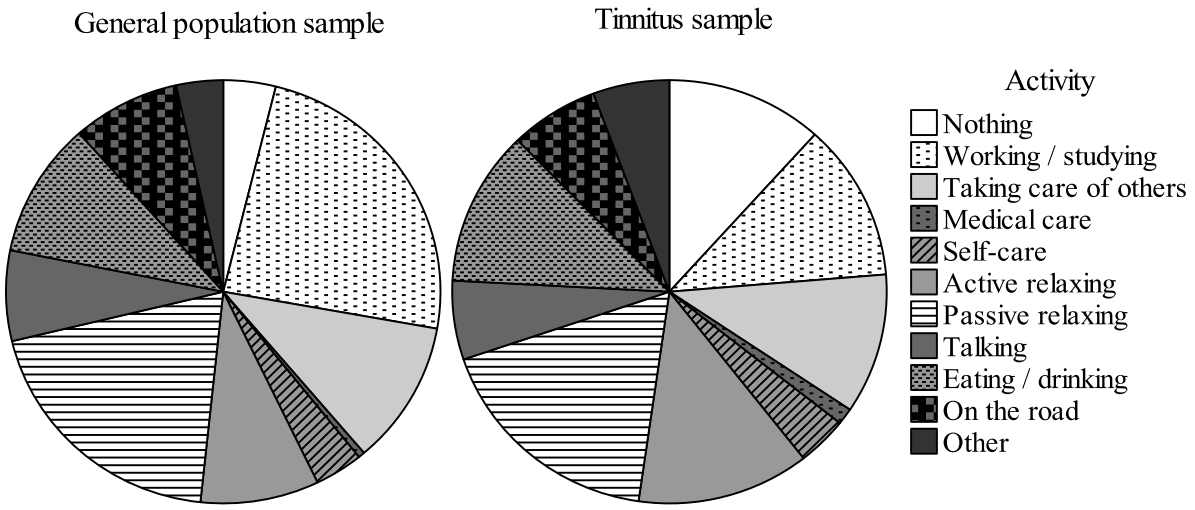


Figure 1. Pie charts representing the percentage of beeps participants registered one of the possible activities

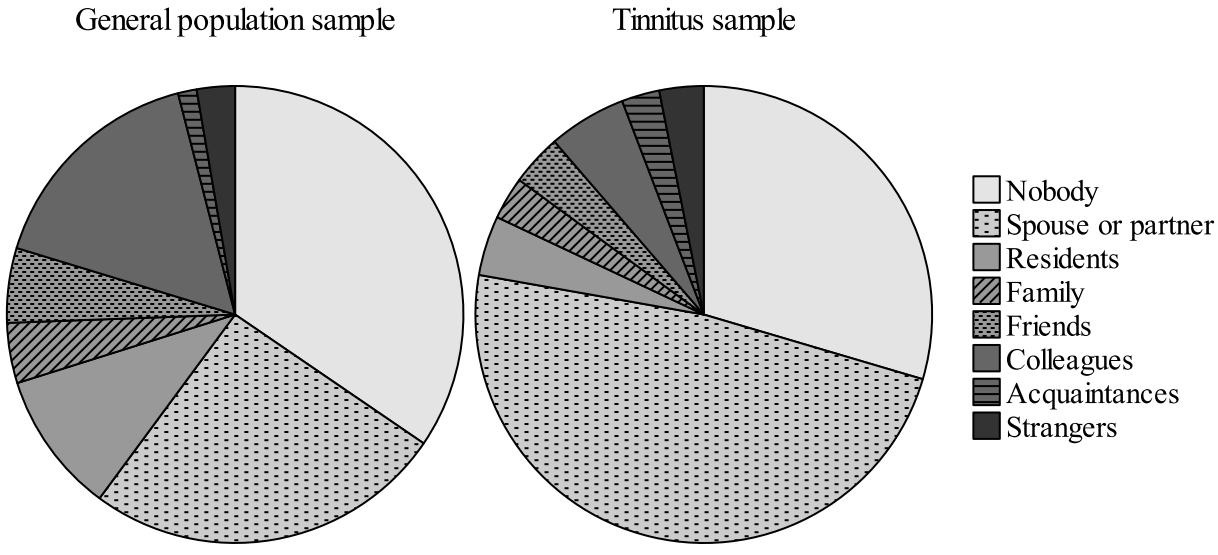


Figure 2. Pie charts representing the percentage of beeps participants registered one of the possible categories of whom they interacted with

Table 3. Results of multilevel analyses investigating the differences between patients with tinnitus and a population based sample with regard to positive affect, negative affect, several physical complaints items, activity level and social interactions.

	Independent variables									
	Group		Sex		Age		Job		Hearing Aid	
	B	SE	B	SE	B	SE	B	SE	B	SE
Dependent variables										
Positive affect	-0.925*	0.387	0.278	0.293	-0.002	0.011	-0.093	0.357	0.591	0.370
Negative affect	0.462**	0.264	0.049	0.205	-0.117	0.008	-0.220	0.249	0.001	0.259
Tinnitus	4.089*	0.387	-0.337	0.293	-0.015	0.011	-0.605**	0.357	0.641**	0.370
Pain	1.038*	0.391	-0.443	0.304	-0.003	0.012	-0.444	0.369	-0.060	0.383
Feeling sick	0.854*	0.372	-0.309	0.289	-0.005	0.011	-0.677**	0.352	0.071	0.361
Tired	1.137*	0.402	-0.757*	0.312	-0.010	0.011	0.024	0.380	-0.268	0.394
Perceived activity level	-0.172	0.401	0.209	0.311	0.015	0.012	0.287	0.378	0.230	0.392
	OR	95% CI	OR	95%CI	OR	95%CI	OR	95% CI	OR	95% CI
Actual activity level	0.745	0.516 1.077	1.131	0.848 1.509	1.004	0.993 1.015	1.526*	1.091 2.163	0.970	0.683 1.376
Social interactions	1.076	0.574 2.018	0.954	0.584 1.560	1.005	0.987 1.024	0.899	0.496 1.629	1.130	0.610 2.096

SE=Standard Error; OR=Odds ratio; CI=Confidence Interval; Hearing aid (0=No; 1=Yes); Group (0=general population; 1=tinnitus); Sex (0=Female; 1=Male); Job (0=No; 1=Yes); Social Interactions (0=Alone; 1=Not alone)

* significant at 5% level; ** significant at 10% level

First, a cross-sectional model based on all beep measurements was tested to determine the extent to which positive affect, negative affect, physical symptoms, activity level and social interactions at one moment (t-1) predicted tinnitus at the next moment (t) (Table 4). In the intercept only model, 67.8% of the variance in tinnitus intensity was explained by between person differences and 32.2% by within person differences. In the final model there was a significant cross-sectional relation between tinnitus intensity, positive affect, pain and tiredness. In this model, 65.8% of the variance was explained by between person differences and 34.2% by within person differences. Second, a prospective model was tested to determine if positive affect, negative affect, physical symptoms, activity level and social interactions (t-1) was related to subsequent tinnitus (t) by including the time-lagged functions of these variables in the model (Table 4). In the intercept only model, 68.3% of the variance in tinnitus intensity was explained by between person difference and 31.7% of the variance by within person differences. In the final model there was a significant positive prospective relation between tinnitus intensity and negative affect and pain. There was a significant negative prospective relation between tinnitus intensity and time-lagged positive affect and pain (t-1). These analyses were corrected for an autoregressive effect of tinnitus. In the final model, 49.1% of the variance in tinnitus intensity was explained by between person differences and 50.9% by within person differences.

Table 4. Variance in tinnitus explained by positive affect, negative affect and pain at one moment (t) and at the previous moment (t-1).

	Model 1 (intercept only)			Final model		
N=1755	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	5.370	0.22	.000	4.777	0.437	.000
Mean PTT at 1,2 and 4 kHz				0.024	.010	.016
Positive affect				-0.130	.028	.000
Negative affect				0.069	.036	.057
Pain				0.061	.019	.002
Tiredness				0.032	.014	.022
Variance	Random			Random		
Person level	1.39			1.25		
Beep level	0.66			0.65		
Model fit	-1859.44			-1837.90		

	Model 1 (intercept only)			Final model		
N=1310	Estimate	SE	P-value	Estimate	SE	P-Value
Intercept	5.376	0.223	.000	2.104	0.252	.000
Mean PTT at 1,2 and 4 kHz				0.011	0.004	.012
Positive affect				-0.087	0.027	.001
Negative affect				0.081	0.034	.018
Lag Tinnitus (t-1)				0.587	0.022	.000
Pain				0.094	0.025	.000
Lag Pain (t-1)				-0.089	0.025	.000
Variance	Random			Random		
Person level	1.40			0.52		
Beep level	0.65			0.54		
Model fit	-1404.99			-1141.28		

PTT=Pure Tone Threshold; kHz=kilohertz; SE=Standard Error

Third, several prospective models were tested to determine if there was a relation between tinnitus (t-1) and subsequent positive affect, negative affect, physical symptoms, activity level and social interactions (t). With regard to positive affect, there was a significant negative association with tinnitus intensity and negative affect and a significant positive association with time lagged tinnitus intensity (t-1) (Table 5). This analysis was controlled for an autoregressive effect of positive affect by including a time-lagged variable of positive affect in the analysis. In the model with pain as dependent variable there was a significant positive association between tinnitus and pain and a significant negative association between time-lagged tinnitus (t-1) and pain (Table 5). For negative affect, there was only a significant association with tinnitus and positive affect at the same moment after controlling for an autoregressive effect of negative affect. There was no prospective association between tinnitus intensity (t-1) and subsequent negative affect (t) (Table 5). No significant effects were found between between tinnitus (t-1) and subsequent tiredness, feeling sick, activity level or social interactions (t).

Discussion

This study reports on the effects of tinnitus on daily life as measured with the ESM. The first part of the study focuses on differences between patients with tinnitus and a general population sample. As expected, patients with tinnitus experienced significantly higher levels of negative affect and physical complaints and lower levels of positive affect. Compared to subjects from a general population sample, patients with tinnitus felt more anxious and insecure and less cheerful, energetic, relaxed and satisfied. These findings are in line with other studies that found elevated anxiety and depression scores on retrospective measures in patients with tinnitus compared to healthy controls or non-help seeking tinnitus sufferers (Attias et al., 1995; Scott & Lindberg, 2000; Stouffer & Tyler, 1990). The difference in reported physical complaints was also expected and could be the result of the increased somatic attention and somatisation in patients with tinnitus which is described in several studies (Hiller et al., 1994; Hiller et al., 1997; Newman et al., 1997). There was a difference between patients with tinnitus and the general population sample in the type of activity they were involved in. Participants from the general population sample more often indicated to be at work, whereas patients with tinnitus more often indicated doing nothing. This difference was especially the result of differences between both samples with regard to having a paid job or not. There were no differences between patients with tinnitus and the general population sample in perceived activity level and actual activity level as measured in daily life. This was not in line with our expectations, since another study reported that tinnitus patients experience difficulties in daily life activities (Cima et al., 2011). Because patients had to choose their actual activity from relatively broad categories there is no exact information on what participants were actually doing, or on the intensity or effortfulness of these activities. Moreover, perceived activity level could reflect the effort that a certain activity poses for an individual. For example, an activity that is rated as low on intensity by a healthy person could be rated as high on intensity by a patient since the activity is more challenging and therefore costing more energy. In future research an actometer could be used to measure the difference in objective activity level between patients with tinnitus and a non-tinnitus control group. With regard to the social interactions no differences were measured between patients with tinnitus and the general population sample in being alone or not. Other studies have shown that patients with tinnitus experience social withdrawal (Folmer et al., 1999; Hiller & Haerkotter, 2005), but this was not confirmed by the present study. However, the results show that patients with tinnitus more often indicated to be with their partner and less often with colleagues and strangers. The difference in time spent with colleagues is probably explained by the fact that there were more participants with a paid job in the general population sample.

Table 5. Variance in positive affect and pain explained by tinnitus at one moment (t) and at the previous moment (t-1).

	Positive affect (dependent variable)					
	Model 1 (intercept only)			Final model		
N=1310	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	5.370	0.218	.000	3.416	0.205	.000
Tinnitus				-0.086	0.025	.000
Lag Tinnitus (t-1)				0.056	0.025	.024
Lag Positive affect (t-1)				0.434	0.023	.000
Negative affect				-0.353	0.029	.000
Variance	Random			Random		
Person level	1.377			.565		
Beep level	0.576			.485		
Model fit	-1240.56			-997.13		

	Negative affect (dependent variable)					
	Model 1 (intercept only)			Final model		
N=1310	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	1.659	0.164	.000	2.082	0.170	.000
Tinnitus				0.043	0.017	.013
Lag Negative affect (t-1)				0.033	0.026	.000
Positive affect				-0.253	0.020	.000
Variance	Random			Random		
Person level	1.032			.494		
Beep level	.0464			.413		
Model fit	-954.35			-787.07		

	Pain (dependent variable)					
	Model 1 (intercept only)			Final model		
N=1310	Estimate	SE	P-value	Estimate	SE	P-value
Intercept	2.336	0.231	.000	0.229	0.141	.105
Tinnitus				0.115	0.030	.000
Lag Pain (t-1)				0.742	0.019	.000
Lag Tinnitus (t-1)				-0.089	0.030	.000
Negative affect				0.136	0.031	.000
Variance						
Person level	1.456			0.318		
Beep level	0.814			0.606		
Model fit	-1681.76			-1259.96		

SE=Standard error

The difference in time spent with strangers could indicate there is less outgoing behavior in patients with tinnitus. In this study no data is available on the intensity of the interactions. It could be that although patients with tinnitus are spending time with other people, they remain in the background and do not actually interact with others. Future research could include more specific questions on the intensity of the social interactions.

The second part of the study focuses on the relations between severity of tinnitus and mood, physical symptoms, activity level and social interactions in patients with tinnitus. The results

show that at moments when tinnitus intensity is experienced as more severe, there is a concomitant increase in other physical symptoms, i.e. pain and fatigue. In addition, more severe tinnitus is accompanied by more negative and less positive mood. No differences were found in activity level or social interaction as a function of tinnitus intensity. The time-lagged analyses indicate that pain has a positive association with tinnitus at the same moment, but a negative association with tinnitus at the following moment. This means that the effect of pain on tinnitus decreases over time which could be an indication of habituation to pain. There was also a reversed temporary effect of tinnitus intensity on subsequent pain and positive affect. That is, there is a positive relation between tinnitus intensity and pain at the same moment, but a negative relation between tinnitus intensity and pain the following moment. With regard to positive affect, there was a negative relation between tinnitus intensity and positive affect at the same moment, but a negative relation between tinnitus intensity and positive affect at the following moment. Thus, the negative effect of tinnitus on pain and positive affect decreases over time, thereby indicating habituation to the tinnitus.

Together these findings suggest that there is no predictive relationship between tinnitus intensity, mood and pain. In contrast, the results indicate that there is some habituation to both pain and tinnitus. It would be interesting to learn whether these habituation effects are stronger in patients who had a treatment aimed at habituation to the tinnitus sound. The observed relations implicate that diagnostics and treatment of tinnitus should not only focus on the severity of the tinnitus but also on the severity of depressive and anxiety complaints as well as on other physical complaints, especially pain.

The current study has some limitations that need to be addressed. Because of the differences in age, sex and having a job, it can not be excluded that these differences have influenced the results. However, the relations were still significant after correcting for these variables. Also, the relations between tinnitus and positive affect, negative affect and physical complaints were confirmed in the within patient analyses, with higher severity of tinnitus being associated with lower levels of positive affect and higher levels of negative affect and physical symptoms.

A second limitation might be in the phrasing of the question on tinnitus intensity at a particular moment. To avoid reactivity, the question was phrased as neutral as possible, i.e. patients indicated whether they experienced tinnitus on a 7-point scale ranging from not at all to very much. This neutral formulation of the item could have triggered patients to interpret the question either as loudness of the tinnitus or as the amount of annoyance caused by the tinnitus. In earlier studies it was shown that tinnitus loudness rarely correlates with experienced distress (Andersson et al., 2005) and only a weak association was found between tinnitus loudness and tinnitus annoyance (Hazell et al., 1985). However, these are correlation studies across individuals and individuals might have their own anchor point for describing loudness (Dauman & Tyler, 1992). Nevertheless, differences in interpretation of tinnitus intensity could have influenced the results. Since a recent study has shown a lack of reactivity in an ESM study as a result of questions about tinnitus annoyance as well as tinnitus loudness, future research could focus on both questions separately (Henry et al., 2012).

Based on the findings above, it can be concluded that tinnitus has a major impact on daily life. Patients suffering from tinnitus experience more emotional and physical complaints than participants from a population based sample, and with increasing tinnitus severity there is a worsening of these complaints. However, there was also evidence of habituation to tinnitus with regard to the effect on positive affect and pain. Future research should shed more light on the temporal relationships and potential causal associations.

SUMMARY AND DISCUSSION

Summary and discussion

The general objective of this thesis was to evaluate the effects of tinnitus on health-related quality of life (HRQOL) and costs. Furthermore, the effects of a specialized, stepped-care cognitive behavioral treatment were compared to care as usual. Chapter 1 to 4 were based on data from a randomized controlled trial (RCT). Chapter 5 and 6 were based on a study using the Experience Sampling Method (ESM) to measure (aspects of) HRQOL in daily life.

Summary of findings

In Chapter 1 health state utility scores of a tinnitus population were elicited using two preference-based health state utility instruments: EurQol-5D (EQ-5D) and Health Utilities Index Mark III (HUI Mark III). These instruments differ in the conceptualization and operationalization of health and the valuation method upon which the utility scores are based. Agreement, construct validity and responsiveness of both measures were examined to determine which utility measure was preferred in a tinnitus population. Corresponding dimensions of both measures showed large correlations, but in the EQ-5D health state description ceiling effects were much more frequently observed. The HUI Mark III utility scores were lower than the EQ-5D utility scores and agreement was poor to moderate. Both the EQ-5D and the HUI Mark III showed evidence of construct validity and both measured statistically significant change in the mean utility scores of improved patients after three months of treatment. The HUI Mark III was the most sensitive to change in the condition. The study concluded that despite considerable overlap between both instruments, the HUI Mark III was considered as the best tool for utility elicitation in patients with tinnitus.

In Chapter 2 the societal cost-of-illness (COI) of tinnitus in the Netherlands was determined. A bottom-up approach was used in which healthcare consumption or cost data were measured by a cost-questionnaire among the patients in a sample and subsequently extrapolated to the total Dutch population. Furthermore, the impact of both disease and demographic characteristics on the healthcare costs and the societal costs were examined. The mean societal cost of illness was €6.7 billion, or €5,315 per patient per year. Sensitivity analyses showed that differences in tinnitus prevalence especially impacted on the societal costs. The healthcare costs ranged from €1.0 billion to €2,9 billion, while the societal costs ranged from €3,3 billion to €10,0 billion. Reported severity of tinnitus was the most important positive predictor of healthcare costs and societal costs. Other significant predictors were duration of complaints, depression scores and age (only for societal costs). We concluded that the economic burden of tinnitus to society is substantial.

In Chapter 3 the effectiveness of a novel specialized stepped-care multidisciplinary treatment protocol (SC) versus Usual Care (UC) for tinnitus was investigated. The first step of the SC included audiological diagnostics and rehabilitation, counseling based on Tinnitus Retraining Therapy, psycho-education and psychological analysis and advice. The second step of SC included counseling, psycho-education, applied relaxation, cognitive behavioral therapy, elements of acceptance and commitment therapy and mindfulness based approaches. The first step of UC consisted mainly of audiological diagnostics and rehabilitation, including the prescription of hearing aids and sound-generators. The second step of UC included one or more consultations with a social worker with a maximum of ten one-hour-sessions, if necessary. A RCT was carried out with 492 adult tinnitus patients of whom 247 were allocated to UC, and 245 to SC. All patients were pre-stratified on tinnitus-severity and hearing impairment. Primary outcomes were HRQOL (HUI Mark III), tinnitus severity (TQ), and tinnitus impairment (THI). Secondary outcomes were negative affect (HADS), catastrophic misinterpretations of the tinnitus sound (TCS) and fear of tinnitus (FTQ). Assessments took place pre-treatment, and at 3, 8 and 12 months after randomization. Multilevel mixed regression was used for intention to treat analyses and showed that SC was

more effective than UC in improving HRQOL and reducing tinnitus severity and tinnitus impairment. Moreover, SC showed more favorable results with regard to improvements in general negative emotional states, level of tinnitus-related catastrophic thinking, and tinnitus-related fear, than UC.

Chapter 4 assessed the cost-effectiveness of SC compared with UC from a societal perspective alongside the above-mentioned RCT. The calculation of the societal costs was based on measurements with a cost-questionnaire and Dutch standard unit prices or other sources if these were not available. Quality-adjusted life years (QALYs) were based on measurements with the HUI Mark III. Total mean bootstrapped costs were €5,636 in UC and €5,921 in SC. Costs associated with the tinnitus care in an audiological centre were considerably higher in SC. This was partly compensated by lower costs in SC for other tinnitus related healthcare costs. Productivity costs were higher in SC. The results showed that SC costs society €19,688 per QALY gained. The probability that SC is cost-effective from a societal perspective was 58% for a willingness-to-pay for a QALY of €35,000. The NICE guideline states that the reimbursement of interventions costing less than £30,000 (approximately € 45,000) is generally never questioned (Devlin & Parkin, 2004; Raftery, 2001). The Dutch Council for Public Health and Health Care has set the threshold at € 80,000 for diseases with a high burden (RVZ, 2006). Based on this SC was considered more cost-effective than UC. However, the uncertainty surrounding the incremental costs and effects was substantial.

Chapter 5 explored the potential value of obtaining momentary, instead of retrospective, accounts of the description and valuation of a person's own health-related quality of life (HRQOL). The study population consisted of 139 participants. To ensure a variety of experienced health states in the study population, participants were recruited from three patient groups (experiencing somatic complaints with a known cause, somatic complaints without a known cause, and psychological complaints) and a general population sample. Momentary HRQOL, positive affect (PA), negative affect (NA) and physical symptoms (PS) were examined with the Experience Sampling Method (ESM). The ESM consists of a beep questionnaire that was administered randomly 10 times a day. Bivariate correlations and multilevel analysis were used to investigate the relation between momentary HRQOL and momentary PA, NA and PS. The relation between momentary outcomes and the EQ VAS was investigated with a multiple regression model. With regard to the feasibility, the overall primary participation rate was low but there were no drop-outs and the number of completed beeps was comparable to other studies. Analysis showed that momentary PA, NA and PS predict the momentary valuation of HRQOL. In addition it was found that these relations are stronger among those with psychological complaints (PA, PS and NA) and tinnitus (PA and PS), than among persons with somatic complaints and the population based sample. Multiple regression analysis showed that if the interaction terms were added to model, none of the momentary feelings and symptoms were significant predictors of retrospective EQ VAS. Also, momentary experienced HRQOL was not a significant predictor of EQ VAS. This supports earlier findings that global reports of past health will rely more on beliefs (semantic memory) than on specific feelings and symptoms (Kahneman et al., 2004; Robinson & Clore, 2002; Stone et al., 2006). We concluded that the use of the ESM to measure accounts of the momentary experience of health in different populations is feasible. The results showed that within persons the valuation of global HRQOL and specific feelings and symptoms are variable from moment to moment. Also, the relation between momentary specific feelings and symptoms and the momentary valuation of HRQOL differed among populations.

In Chapter 6 the aim was to compare patients with tinnitus to a non-tinnitus control sample with regard to emotions, activities and social interactions in daily life as measured with the ESM. Although there is some knowledge on these relation based on previous research, these

studies have all relied on retrospective assessment of past experiences which is can be prone to several types of bias (Robinson & Clore, 2002; Stiggelbout & de Vogel-Voogt, 2008). Within patients with tinnitus the associations between effects of tinnitus severity and the level of PA, NA, PS, activity and social interactions in daily life were examined. Forty patients with tinnitus and a convenience (control) sample of 40 persons were included in this study. Multilevel regression analysis confirmed a significant difference between the samples with regard to PA, NA and PS, but not with regard to activities or social interactions. When tinnitus intensity is experienced as more severe, there is a concomitant increase in pain and fatigue. In addition, more severe tinnitus is accompanied by more negative and less positive mood. The time-lagged analyses indicate that pain has a positive association with tinnitus at the same moment, but a negative association with tinnitus at the following moment. This means that the effect of pain on tinnitus decreases over time which could be an indication of habituation to pain. Furthermore, there was a reversed temporary effect of tinnitus intensity on subsequent pain and positive affect. This means that the negative effect of tinnitus on pain and positive affect decreases over time, thereby indicating habituation to the tinnitus. It can be concluded that tinnitus has a major impact on emotions and symptoms in daily life.

Discussion

Economic burden

Tinnitus treatment has been frequently described as costly to both the patients who suffer from it and the society at large (Henry et al., 2005; Lockwood et al., 2002; Reich, 2002). However, up till now there was no empirical evidence to sustain these statements. In Chapter 2 the first study to examine the costs of illness of tinnitus from a societal perspective was described. The sample included in this study might not be representative for the total tinnitus population since it was a help seeking population in one single audiological centre in the south of the Netherlands. However, sensitivity analysis showed that even when the data were extrapolated to the total population based on more conservative prevalence figures, the burden to society was substantial. Nevertheless, COI studies in broader defined tinnitus populations (regarding level of severity, help seeking, part of the Netherlands) are needed to check the generalizability of our results.

COI studies are important to inform decision makers on the economic burden of a disease. Although its usefulness as a decision-making tool in resource allocation has been questioned, it can be useful in drawing decision-makers interest for conditions whose burden has been somehow underestimated (Tarricone, 2006). This might also be the case for a condition like tinnitus, which is often described as a symptom and not a disease (Noell & Meyerhoff, 2003) and might therefore not be recognized as a formal diagnosis. In 2010 The Dutch Health Care Insurance Board (CVZ) decided that multidisciplinary tinnitus treatment was not covered by the Health Care Insurance Act (CVZ, 2010). Tinnitus treatments that are covered by the Health Insurance Act are scarce and non-evidence based, as these include the prescription of sound maskers for which no clear evidence of efficacy has been found (Hobson et al., 2012). The results of our study (Chapter 2) showed that the economic burden of tinnitus to society is substantial. Implementing a cost-effective treatment could improve healthcare resource allocation. Our study also showed that the reported severity of tinnitus is an important predictor of the costs that patients make. Other significant predictors of costs were shorter duration of tinnitus and more severe depression. This implies that adequate referral and early intervention are necessary in order to prevent tinnitus and depression becoming more severe, thereby inflating the costs of tinnitus.

Health-related quality of life

In Chapter 1, the EQ-5D and the HUI Mark III showed evidence of construct validity and both measures were able to detect a statistically significant change in the mean utility scores of improved patients after three months of treatment. However, the effect sizes were small and the chance of being able to distinguish between improved and unimproved patients was only 61% in the HUI Mark III and 58% in the EQ-5D. Since this was the first study to determine which utility measure would be preferred in a tinnitus population, more research is necessary to check the reproducibility of our results. Also, other multi-attribute utility measures, like for instance the SF-6D (Brazier et al., 2002), ICECAP-A (Al-Janabi et al., 2011; Al-Janabi et al., Published online ahead of print Oct, 2012) and Quality of Well-Being Scale (Kaplan & Anderson, 1988) are available. To our knowledge, these instruments have not been tested in tinnitus patients. A comparative review of different multi-attribute utility measures instruments did not find a uniformly best performing instrument and it was suggested to base the instrument selection on the characteristics that are most relevant to the particular measurement needs (Coons et al., 2000). In the case of tinnitus both the HUI Mark III and the SF-6D include dimensions that are relevant for measuring change after tinnitus treatment. The SF-6D addresses physical, mental and social functioning while the HUI Mark III includes impairments in hearing, emotion and cognition among other things. The SF-6D might have been more responsive than the instruments used in our study, since increasing physical, mental and social functioning was ultimately the focus of treatment, especially in the SC. Improvements in cognition and hearing as measured by the HUI Mark III were also a desired effect of treatment but not the main focus. However, more research is necessary to assess the responsiveness of the SF-6D in a population with tinnitus. Moreover, the validity of multi-attribute utility instruments that result in a population preference for health can be questioned. When these instruments are used it is assumed that members of the public are able to imagine what it would be like if they were experiencing a certain health state. Several authors have discussed different types of problems that could lead to biases when multi-attribute measures or direct utility measures such as the time trade-off (TTO) are used to determine health state utilities (Robinson & Clore, 2002; Stiggelbout & de Vogel-Voogt, 2008). It was suggested that measuring experienced utility by studying actual momentary experience of a health state with the ESM, could solve these problems (Kahneman et al., 1997). However, when performing a cost-effectiveness analysis from a societal perspective, preference for different health states are preferably derived from the general population (Gold et al., 1996; Torrance et al., 1996). Since experienced utility can only be derived from a person who is actually experiencing a health state, it is no longer possible to perform an economic evaluation from a societal perspective. A two-step procedure to inform those doing ex ante health state preferences about the descriptions of patients based on experienced utility was suggested (Drummond et al., 2009). However this does not solve the problems regarding a focusing illusion (Stiggelbout & de Vogel-Voogt, 2008; Ubel et al., 2001). The focusing illusion is a bias that leads subjects to focus disproportionately on what would be different between their own health state and the health state under investigation. On the other hand, data on experienced utility collected with the ESM is also able to give a more detailed description of the influence of a certain health state on daily life than other generic health-related quality of life measures. Future research should focus on the use of ESM data to inform those doing ex ante health state preferences and the impact of this information on the eventual health state evaluation.

In Chapter 5 we reported on the results of a study that, to our knowledge for the first time, used the Experience Sampling Method (ESM) to obtain accounts of the momentary experience of HRQOL (overall HRQOL, PA, NA, PS). A global retrospective valuation of HRQOL was not predicted by momentary feelings, symptoms and HRQOL. This highlights

that retrospective measures may provide a biased account of the impact of health problems in the daily lives of people who are affected. Moreover, the bias may be different in different conditions. Given the relation between momentary experienced HRQOL and momentary PA, NA and PS, it is expected that the ESM is able to detect changes over time, but this has to be confirmed in future research. It is unclear how the results of our effectiveness and cost-effectiveness study would have been affected if we would have used momentary experienced HRQOL as measured with the ESM as an outcome measure instead of retrospective global measures of HRQOL such as the EQ-5D. More research is necessary to determine the ability of the ESM for detecting changes in HRQOL over time for use in (cost-)effectiveness research.

Effectiveness and cost-effectiveness of treatment

In the RCT the effectiveness of SC as compared to UC was investigated. Although one of the treatment arms was designed to represent usual care in a Dutch audiological centre, it is very likely that this therapy does not fully represent the therapy that is usually offered to tinnitus patients in the Netherlands. Current usual care practices often result in communicating to patients that nothing can be done about the tinnitus, but learn to live with it (Cima et al., 2009). A considerable proportion of the patients might not be referred to an audiological centre or an ENT specialist at all. This made it difficult to identify care as usual in this population of patients who seek help in different levels of health care. The advantage of including patients in an audiological centre, instead of for instance a general practitioner is that patients could be stratified on hearing loss and tinnitus severity thereby ensuring an equal allocation to both treatment arms.

Another important consideration that has to be taken into account when evaluating the results of this RCT is the fact that SC consisted of several elements and it is unclear which of these elements have contributed most to the overall effectiveness. For example, it has been suggested that TRT has no additional beneficial effects as an additional treatment approach to CBT. On the other hand there are also elements that are not explicitly part of the treatment that could have contributed to the overall effectiveness, like for instance peer contact. To get more insight into the effectiveness of the different elements in SC as evaluated in the RCT described in this thesis, future studies should adopt a dismantling approach leaving out potentially redundant treatment components in subsequent trials thereby fine-tuning current treatment strategies.

The ESM study described in chapter 6 has shown that tinnitus is associated with many problems and interferences in daily life. It is expected that the SC based on cognitive behavioral therapy is effective in reducing these problems as was also evidenced by the significant decrease in tinnitus impairment. Although more research is necessary to determine temporal relationships and potential causal associations between tinnitus severity, mood and physical symptoms, the observed relations implicate that diagnosis and treatment of tinnitus should not only focus on the severity of the tinnitus but also on the severity of depressive and anxiety complaints as well as on physical complaints. Post-hoc analyses of the trial data that were published separately, have shown that addressing tinnitus-related fear and fear-responses, which is part of SC, is important in the management of patients with disabling tinnitus (Cima, 2013).

Another consideration with regard to the results of the RCT relates to the fact that the study was done in an outpatient clinic for audiological rehabilitation where different disciplines have the ability to work integrally. As a result, it is unclear whether the results can be generalised to other healthcare settings and whether this might be a threat for implementing SC across these settings. More research into the effective elements of treatment could assist the development of implementation strategies tailored to different healthcare settings.

The results of the cost-effectiveness analysis showed that SC costs society €19,688 per QALY gained based on the base case estimates of input parameters. The SC was considered more cost-effective than UC despite that the uncertainty surrounding the incremental costs and effects was substantial. However, this is the first cost-effectiveness analysis alongside a randomized clinical trial (RCT) in tinnitus treatment and decision-makers need to be informed about costs and effects for the full range of alternative interventions as a basis for decision-making (Sculpher et al., 2006). Therefore, more RCTs need to be conducted in the field of tinnitus treatment to adequately inform decision makers.

The time horizon in the RCT described in this thesis was relatively short: 12 months. Other studies found that treatments based on TRT or CBT, which were an important part of SC, were effective up to 15 years after the therapy ended (Forti et al., 2009; Goebel et al., 2006; Lux-Wellenhof & Hellweg, 2002; Zachriat & Kroner-Herwig, 2004). This may imply that the effectiveness and cost-effectiveness of SC is underestimated. Currently, we are investigating the long-term effects and costs of treatment at three and five years after baseline. With regard to the costs, not only a cost-questionnaire with a three-month recall period was administered but also large expenses since the end of trial were recorded. It is expected that patients in the SC group have less expenses than patients in the UC group.

There are some other factors that need to be considered when interpreting the results of the economic evaluation. First, incremental effectiveness was determined by using a generic health-related quality of life measure. In the previous section it was already discussed that the HUI Mark III might not have been responsive enough to detect changes as a result of the treatment. It is expected that the use of a disease specific preference based instrument would have resulted in more favourable results for SC. However, for tinnitus such an instrument is not available. The Tinnitus Disability Index (TDI) (Cima et al., 2011), a self-report measure for disability due to tinnitus on daily life activities, might be a useful instrument as an outcome measure in CEA. The questionnaire consists of 7 items corresponding to 7 major dimensions of daily life, which have to be rated on a horizontal VAS (0-10) anchored as 0 corresponding to ‘no disability’ and 10 to ‘total disability’. To develop a preference based measure this answering scale needs to be reduced into several levels. Then, a time trade-off or standard gamble study should be conducted in the general public to obtain weights associated with the dimensions and levels of this questionnaire. Using such an instrument as a tool to aid decision-making for resource allocation decisions only has value if all studies evaluating the cost-effectiveness of tinnitus treatments would use this measure of outcome. This way, the relative effectiveness of new tinnitus treatments could be evaluated. However, the disadvantage of using disease specific utility instruments is that decision makers cannot make any comparisons across diseases. Moreover, as a threshold for ‘a year without tinnitus disability’ is lacking, it is impossible to judge whether a tinnitus treatment would be cost-effective or not.

Second, there may be elements that did not have any contribution to the overall effectiveness, like for instance the prescription of tinnitus maskers. Evidence regarding the effectiveness of these expensive devices in tinnitus treatment is not clear (Hobson et al., 2012) and might have had a negative influence on the overall cost-effectiveness of SC. Another cost saving might result from dividing the first step of treatment into smaller steps. At this time, in SC every patient receives a counseling session with a clinical physicist in audiology, an intake with a clinical psychologist and an educational group session. The question is whether this extensive first level is needed for patients that report a mild tinnitus at baseline. Perhaps these patients just need some reassurance that the tinnitus is not the result of some kind of serious deficit. Furthermore, although patients in the second level of SC were advised to resume their paid work only after the intervention was completed, there is no scientific evidence that earlier

return to work would have a negative impact on the effectiveness of treatment. When these issues would be taken into consideration, SC may be more cost-effective.
Recent interventions that investigated the effectiveness of alternative treatment strategies in tinnitus treatment include drug therapy (Elgoyhen & Langguth, 2012; Langguth & Elgoyhen, 2012), neurological brain stimulation (Meng et al., 2011) or cochlear implants (Arts et al., 2012). Results indicate benefits of these treatment to be absent, minor or particular to a small group of patients. There is no evidence regarding the cost-effectiveness of these treatments, but some of them are thought to be more expensive than SC like for instance neurological brain stimulation and cochlear implants. The additional effects of these treatments therefore need to be considerable to compensate for the expected higher costs.

Areas for future research

Economic burden

A problem in bottom-up COI studies is that cost-questionnaires entirely rely on the patient's memory and also on the patient's judgment of which costs are related to the tinnitus and which costs are not. Another option for measuring healthcare utilization and costs is the use of cost diaries. However, problems with this method like for instance low completion rates were reported (Wolfs et al., 2009). This problem could be solved by being able to prompt patients to answer a set of questions about resource use in close proximity to the event. The ESM described in chapter 5 and 6 could not only be of use in measuring HRQOL in daily life but also in determining resource use. Applications for an ESM device or mobile phones could be used to prompt patients on a daily basis to fill out their resource use and costs with regard to the tinnitus. Further research could focus on determining the optimal ESM period and frequency has to be determined to ensure the inclusion of all relevant costs as well as adherence to the study.

Experience Sampling Method in economic evaluation

There are some challenges that need to be addressed before utility data based on the ESM can be used as an outcome variable in economic evaluations of health care.
First, momentary HRQOL data collected during the ESM week needs to be expressed into one single utility score to be useful for assessing cost-effectiveness of different treatments. Currently we are investigating different ways to aggregate ESM data into a utility score by using duration-weighting approaches. One example is the U-index, which was suggested by Kahneman and Krueger (2006). The U-index looks at the highest rating (if this is a negative feeling, the time in that activity is scored as one; otherwise it is scored as zero) and then calculates the proportion of time that people spend in an unpleasant state. The ability of such an index to detect changes over time needs to be determined in future prospective studies.
Second, the conceptualisation of HRQOL as part of the ESM needs to be evaluated. In our study HRQOL was assessed with a question anchored in the same way as the EQ-5D VAS. The question remains whether this item accurately measures HRQOL or whether other data in the ESM can be aggregated to an experienced utility score, like for instance the ability of a person to perform their daily activities, to engage in social interactions and their overall PA, NA and PS.
Third, although using the ESM is advocated to overcome challenges regarding different types of bias in retrospective measures, recent literature has stressed the conceptual differences between momentary and global assessment (Tay et al., in press). Momentary reports reflect current affective or physical states, whereas global assessment is based upon some self-reflection processes like introspection and self-observation. In other words, global assessments of HRQOL rely more on general beliefs, whereas momentary reports rely on experience (Schwarz et al., 2009). From this point of view, one method is not necessarily

superior to the other but instead they might complement each other. Future research should focus on the use of a multi-method perspective that incorporates all relevant information for determining HRQOL as an outcome measure in economic evaluation of health care.
Finally, the ESM has previously been described as time-consuming and invasive and it was suggested that these problems could be solved by using the Day Reconstruction Method (DRM) (Kahneman et al., 2004). In the DRM respondents are asked to divide the previous day into a number of episodes and to then rate several mood and contextual items for each episode (Kahneman et al., 2004). Although, evidence was provided that DRM data is a good approximation for ESM data when measuring mood (Kahneman et al., 2004), there is also evidence that the correlations between both methods is only moderate (Tay et al., in press). In our study on the use of the ESM in measuring HRQOL, the DRM was also administered. We are currently analyzing whether the DRM would be a good approximation of the ESM in measuring HRQOL. However, even when this is the case one should keep in mind that the ESM aims to capture event-based experiences, while the DRM aims to approximate momentary experiences through daily retrospective reporting (Tay et al., in press). Furthermore, it is questionable whether participants indeed thought the DRM to be less invasive. In our ESM study, the participants were asked to fill out beep questionnaires 10 times a day for a period of 6 days. This may seem as a large burden, but it took participants only 2 minutes to complete a beep questionnaire, probably because they did not have to rely on their memory. Also, the drop out percentage was satisfactory and in most participants the ESM did not influence their mood or daily routines. Completing the DRM took the respondents in our study on average 2,5 hours (data on file). Further research is necessary to determine the relative burden of both methods by asking patients in future research which method they prefer.

Conclusion

Overall, we can conclude that the burden of tinnitus should not be underestimated. Not only does tinnitus have an impact on quality of life, mood and physical symptoms, it is also associated with high costs. Both the healthcare costs and the societal costs increase with increasing tinnitus severity. Adequate treatment is therefore imperative. SC is a promising intervention that is not only effective when compared to UC, but also cost-effective. It is important to further investigate which elements of SC have contributed to the overall effectiveness and which have not, to improve (cost-)effectiveness and implementation. Furthermore, we can conclude that the ESM is a promising new method for measuring momentary experienced HRQOL for use in comparative effectiveness research and economic evaluations although there are still issues that need to be addressed in future studies.

REFERENCES

Acarturk, C., Smit, F., de Graaf, R., van Straten, A., Ten Have, M., & Cuijpers, P. (2009). Economic costs of social phobia: a population-based study. *Journal of Affective Disorders 115*(3), 421-429.

Adams, P.F., Hendershot, G.E., & Marano, M.A. (1999). Current estimates from the National Health Interview Survey, 1996. *Vital and Health Statisitics 10*(200), 1-203.

Ahmad, N., & Seidman, M. (2004). Tinnitus in the older adult: epidemiology, pathophysiology and treatment options. *Drugs & Aging, 21*(5), 297-305.

Al-Janabi, H., Flynn, T.N., & Coast, J. (2011). Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. *Qual Life Res, 21*(1), 167-176.

Al-Janabi, H., Peters, T.J., Brazier, J., Bryan, S., Flynn, T.N., Clemens, S. (Published online ahead of print Oct, 2012). An investigation of the construct validity of the ICECAP-A capability measure. *Qual Life Res*.

Andersson, G. (2002). Psychological aspects of tinnitus and the application of cognitive-behavioral therapy. *Clinical Psychology Review, 22*(7), 977-990.

Andersson, G., Baguley, D.M., McKenna, L., & McFerran, D. (2005). *Tinnitus: a multidisciplinary approach*. London: Whurr Publishers Ltd.

Arts, R.A., George, E.L., Stokroos, R.J., & Vermeire, K. (2012). Review: cochlear implants as a treatment of tinnitus in single-sided deafness. *Curr Opin Otolaryngol Head Neck Surg, 20*(5), 398-403.

Attias, J., Shemesh, Z., Bleich, A., Solomon, Z., Bar-Or, G., Alster, J. (1995). Psychological profile of help-seeking and non-help-seeking tinnitus patients. *Scandinavian Audiology, 24*(1), 13-18.

Axelsson, A., & Ringdahl, A. (1989). Tinnitus--a study of its prevalence and characteristics. *British Journal of Audiology, 23*(1), 53-62.

Badia, X., Monserrat, S., Roset, M., & Herdman, M. (1999). Feasibility, validity and test-retest reliability of scaling methods for health states: the visual analogue scale and the time trade-off. *Quality of Life Research, 8*(4), 303-310.

Baguley, D.M., Humphriss, R.L., & Hodgson, C.A. (2000). Convergent validity of the tinnitus handicap inventory and the tinnitus questionnaire. *The Journal of Laryngology & Otology 114*(11), 840-843.

Bartels, H., Middel, B.L., van der Laan, B.F., Staal, M.J., & Albers, F.W. (2008). The additive effect of co-occurring anxiety and depression on health status, quality of life and coping strategies in help-seeking tinnitus sufferers. *Ear & Hearing, 29*(6), 947-956.

Barton, G.R., Bankart, J., Davis, A.C., & Summerfield, Q.A. (2004). Comparing Utility Scores Before and After Hearing-Aid Provision : Results According to the EQ-5D, HUI3 and SF-6D. *Applied Health Economics and Health Policy, 3*(2), 103-105.

Barton, G.R., Sach, T.H., Avery, A.J., Jenkinson, C., Doherty, M., Whynes, D.K. (2008). A comparison of the performance of the EQ-5D and SF-6D for individuals aged >or= 45 years. *Health Economics, 17*(7), 815-832.

Berger, A., Dukes, E., Martin, S., Edelsberg, J., & Oster, G. (2007). Characteristics and healthcare costs of patients with fibromyalgia syndrome. *International Journal of Clinical Practice 61*(9), 1498-1508.

Bharmal, M., & Thomas, J., 3rd. (2006). Comparing the EQ-5D and the SF-6D descriptive systems to assess their ceiling effects in the US general population. *Value in Health, 9*(4), 262-271.

Blough, D.K., Ramsey, S., Sullivan, S.D., & Yusen, R. (2009). The impact of using different imputation methods for missing quality of life scores on the estimation of the cost-effectiveness of lung-volume-reduction surgery. *Health Economics, 18*(1), 91-101.

Boonen, A., van den Heuvel, R., van Tubergen, A., Goossens, M., Severens, J.L., van der Heijde, D. (2005). Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Annals of the Rheumatic Diseases 64*(3), 396-402.

Bradburn, N., Sudman, S., & Wansink, B. (2004). *Asking questions (2nd)*. San Francisco: Jossey Bass.

Brazier, J., Roberts, J., & Deverill, M. (2002). The estimation of a preference-based measure of health from the SF-36. *J Health Econ, 21*(2), 271-292.

Brazier, J., Roberts, J., Tsuchiya, A., & Busschbach, J. (2004). A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Economics, 13*(9), 873-884.

Briggs, A.H., Wonderling, D.E., & Mooney, C.Z. (1997). Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. *Health Economics, 6*(4), 327-340.

Brooks, R. (1996). EuroQol: the current state of play. *Health Policy, 37*(1), 53-72.

Burt, D.B., Zembar, M.J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychol Bull, 117*(2), 285-305.

Central Bureau of Statistics. (2009). Statline: http://www.cbs.nl/nl/statline/index.htm.

Cima, R., Joore, M., Maes, I., Scheyen, D., Refaie, A.E., Baguley, D.M. (2009). Cost-effectiveness of multidisciplinary management of Tinnitus at a specialized Tinnitus centre. *BMC Health Services Research 9*, 29.

Cima, R.F., Crombez, G., & Vlaeyen, J.W. (2011). Catastrophizing and fear of tinnitus predict quality of life in patients with chronic tinnitus. *Ear Hear, 32*(5), 634-641.

Cima, R.F., Vlaeyen, J.W., Maes, I.H., Joore, M.A., & Anteunis, L.J. (2011). Tinnitus interferes with daily life activities: a psychometric examination of the Tinnitus Disability Index. *Ear Hear, 32*(5), 623-633.

Cima, R.F., Maes, I.H., Joore, M.A., Scheyen, D.J., El Refaie, A., Baguley, D.M. (2012). Specialized treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. *Lancet, 379*(9830), 1951-1959.

Cima, R.F. (2013). *Tinnitus. A CBT-based approach.* (PhD), Maastricht University, Maastricht.

Cohen, J. (1988). *Statistical power analysis for behavioral sciences.* Hillsdale, N.J.: Lawrence Erlbaum Associates.

Colman, A.M., Norris, C.E., & Preston, C.C. (1997). Comparing rating scales of different lengths: Equivalence of Scores From 5-Point and 7-Point Scales. *Psychological Reports, 80*(355-362).

Conner TS, Tennen H, Fleeson W, Barrett LF (2009). Experience Sampling Methods: A Modern Idiographic Approach to Personality Research. *Soc Personal Psychol Compass. 1;3*(3), 292-313.

Coons, S.J., Rao, S., Keininger, D.L., & Hays, R.D. (2000). A comparative review of generic quality-of-life instruments. *Pharmacoeconomics, 17*(1), 13-35.

Cronan, T., Serber, E.R., & Walen, H.R. (2002). Psychosocial predictors of health status an helath care costs among people with fibromyalgia. *Anxiety, Stress and Coping, 15*(3), 261-274.

CVZ. (2010). Multidisciplinar treatment program for subjective tinnitus is not included among the provisions insured on the grounds of the Zvw. Retrieved July 20th, 2013, from http://www.cvz.nl/

Dauman, R., & Tyler, R. S. (1992). Some considerations on the classification of tinnitus. In R. Dauman & J. M. Aran (Eds.), *Tinnitus 91 - Proceedings of the Fourth International Tinnitus Seminar* (pp. 225-229). Amsterdam: Kugler Publications.

Davis, A., & El Refaie, A. (2000). *Epidemiology of tinnitus*. San Diego: Singular.

Delespaul, P.A.E.G. (1995). *Assessing schizophrenia in daily life - the experience sampling method* Maastricht: Maastricht University Press.

Devlin, N., & Parkin, D. (2004). Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Economics, 13*(5), 437-452.

Dolan, P. (1997). Modeling valuations for EuroQol health states. *Medical Care, 35*(11), 1095-1108.

Drummond, M., Brixner, D., Gold, M., Kind, P., McGuire, A., & Nord, E. (2009). Toward a consensus on the QALY. *Value in Health, 12 Suppl 1*, S31-35.

Drummond, M.F., Sculpher, M.J., Torrance, G.W., O'Brien, B.J., & Stoddart, G.L. (2005). *Methods for the economic evaluation of health care programmes*. New York: Oxford University Press.

Efron, B., & Tibshirani, R. (1993). *An introduction to the bootstrap*. Londen: Chapmann & Hall.

El Refaie, A., Davis, A., Kayan, A., Baskill, J., Lovell, E., & Owen, V. (2004). A questionnaire study of the quality of life and quality of family life of individuals complaining of tinnitus pre- and post-attendance at a tinnitus clinic. *International Journal of Audiology, 43*(7), 410-416.

Elgoyhen, A.B., & Langguth, B. (2012). Pharmacological approaches to the treatment of tinnitus. *Drug Discov Today, 15*(7-8), 300-305.

Erlandsson, S.I., & Hallberg, L.R. (2000). Prediction of quality of life in patients with tinnitus. *British Journal of Audiology, 34*(1), 11-20.

Erlandsson, S.I., Rubinstein, B., Axelsson, A., & Carlsson, S.G. (1991). Psychological dimensions in patients with disabling tinnitus and craniomandibular disorders. *British Journal of Audiology, 25*(1), 15-24.

Espallargues, M., Czoski-Murray, C.J., Bansback, N.J., Carlton, J., Lewis, G.M., Hughes, L.A. (2005). The impact of age-related macular degeneration on health status utility values. *Investigative Ophthalmology & Visual Science, 46*(11), 4016-4023.

Feeny, D., Furlong, W., Boyle, M., & Torrance, G.W. (1995). Multi-attribute health status classification systems. Health Utilities Index. *Pharmacoeconomics, 7*(6), 490-502.

Feeny, D., Furlong, W., Torrance, G.W., Goldsmith, C.H., Zhu, Z., DePauw, S. (2002). Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. *Medical Care, 40*(2), 113-128.

Feeny, D., Wu, L., & Eng, K. (2004). Comparing short form 6D, standard gamble, and Health Utilities Index Mark 2 and Mark 3 utility scores: results from total hip arthroplasty patients. *Quality of Life Research, 13*(10), 1659-1670.

Fisk, J.D., Brown, M.G., Sketris, I.S., Metz, L.M., Murray, T.J., & Stadnyk, K.J. (2005). A comparison of health utility measures for the evaluation of multiple sclerosis treatments. *Journal of Neurology, Neurosurgery & Psychiatry, 76*(1), 58-63.

Folmer, R.L., Griest, S.E., & Martin, W.H. (2001). Chronic tinnitus as phantom auditory pain. *Otolaryngology - Head and Neck Surgery 124*(4), 394-400.

Folmer, R.L., Griest, S.E., Meikle, M.B., & Martin, W.H. (1999). Tinnitus severity, loudness, and depression. *Otolaryngol Head Neck Surg, 121*(1), 48-51.

Forti, S., Costanzo, S., Crocetti, A., Pignataro, L., Del Bo, L., & Ambrosetti, U. (2009). Are results of tinnitus retraining therapy maintained over time? 18-month follow-up after completion of therapy. *Audiology and Neurotology, 14*(5), 286-289.

Goebel, G., Kahl, M., Arnold, W., & Fichter, M. (2006). 15-year prospective follow-up study of behavioral therapy in a large sample of inpatients with chronic tinnitus. *Acta Otolaryngology Suppl*(556), 70-79.

Gold, M.R., Siegel, J.E., & Russell, L.B. (1996). *Cost-effectiveness in health and medicine*. New York: Oxford University Press.

Gore, M., Sadosky, A., Stacey, B.R., Tai, K.S., & Leslie, D. (2012). The burden of chronic low back pain: clinical comorbidities, treatment patterns, and health care costs in usual care settings. *Spine (Phila Pa 1976), 37*(11), E668-677.

Grieve, R., Grishchenko, M., & Cairns, J. (2008). SF-6D versus EQ-5D: reasons for differences in utility scores and impact on reported cost-utility. *The European Journal of Health Economics*

Gross Protney, L., & Watkins, M.P. (1993). *Foundations of clinical research*. Norwalk: Appleton & Lange.

Grutters, J.P., Joore, M.A., van der Horst, F., Verschuure, H., Dreschler, W.A., & Anteunis, L.J. (2007). Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. *Quality of Life Research, 16*(8), 1439-1449.

Gudex, C., Skellgaard, P.H., West, T., & Sorensen, J. (2009). Effectiveness of a tinnitus management programme: a 2-year follow-up study. *BMC Ear Nose Throat Disorders, 9*, 6.

Hakkaart - van Roijen, L., Tan, S.S., & Bouwmans, C.A.M. (2010). *Manual for costing research (in Dutch)*. Amstelveen: College voor zorgverzekeringen.

Hallam, R.S., Jakes, S.C., & Hinchcliffe, R. (1988). Cognitive variables in tinnitus annoyance. *British Journal of Clinical Psychology, 27 (Pt 3)*, 213-222.

Hallam, R.S., McKenna, L., & Shurlock, L. (2004). Tinnitus impairs cognitive efficiency. *Int J Audiol, 43*(4), 218-226.

Hatoum, H.T., Brazier, J.E., & Akhras, K.S. (2004). Comparison of the HUI3 with the SF-36 preference based SF-6D in a clinical trial setting. *Value in Health, 7*(5), 602-609.

Hays, R.D., Sherbourne, C.D., & Mazel, R.M. (1993). The RAND 36-Item Health Survey 1.0. *Health Econ, 2*(3), 217-227.

Hazell, J.W., Wood, S.M., Cooper, H.R., Stephens, S.D., Corcoran, A.L., Coles, R.R. (1985). A clinical study of tinnitus maskers. *Br J Audiol, 19*(2), 65-146.

Hedeker D, Mermelstein RJ, & H, D. (2012). Modeling between-subject and within-subject variances in ecological momentary assessment data using mixed-effects location scale models. *Statistics in Medicine, 31*(27), 3328-3336.

Heller, A.J. (2003). Classification and epidemiology of tinnitus. *Otolaryngol Clin North Am, 36*(2), 239-248.

Henry, J.A., Dennis, K.C., & Schechter, M.A. (2005). General review of tinnitus: prevalence, mechanisms, effects, and management. *Journal of Speech Language and Hearing Research, 48*(5), 1204-1235.

Henry, J.A., Galvez, G., Turbin, M.B., Thielman, E.J., McMillan, G.P., & Istvan, J.A. (2012). Pilot study to evaluate ecological momentary assessment of tinnitus. *Ear Hear, 33*(2), 179-290.

Henry, J.A., Loovis, C., Montero, M., Kaelin, C., Anselmi, K.A., Coombs, R. (2007). Randomized clinical trial: group counseling based on tinnitus retraining therapy. *Journal of Rehabilitation Research and Development, 44*(1), 21-32.

Henry, J.A., Schechter, M.A., Nagler, S.M., & Fausti, S.A. (2002). Comparison of tinnitus masking and tinnitus retraining therapy. *Journal of the American Academy of Audiology, 13*(10), 559-581.

Herraiz, C., Hernandez, F.J., Toledano, A., & Aparicio, J.M. (2007). Tinnitus retraining therapy: prognosis factors. *American Journal of Otolaryngology, 28*(4), 225-229.

Hesser, H., Weise, C., Westin, V.Z., & Andersson, G. (2011). A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress. *Clinical Psychology Review, 31*(4), 545-553.

Hiller, W., Goebel, G., & Rief, W. (1994). Reliability of self-rated tinnitus distress and association with psychological symptom patterns. *Br J Clin Psychol, 33 (Pt 2)*, 231-239.

Hiller, W., & Haerkotter, C. (2005). Does sound stimulation have additive effects on cognitive-behavioral treatment of chronic tinnitus? *Behav Res Ther, 43*(5), 595-612.

Hiller, W., Janca, A., & Burke, K.C. (1997). Association between tinnitus and somatoform disorders. *J Psychosom Res, 43*(6), 613-624.

Hoare, D.J., Gander, P.E., Collins, L., Smith, S., & Hall, D.A. (2010). Management of tinnitus in English NHS audiology departments: an evaluation of current practice. *Journal of Evaluation in Clinical Practice*.

Hobson, J., Chisholm, E., & El Refaie, A. (2010). Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database Syst Rev*(12), CD006371.

Hobson, J., Chisholm, E., & El Refaie, A. (2012). Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database Syst Rev, 11*, CD006371.

Hopewell, S., Clarke, M., Moher, D., Wager, E., Middleton, P., Altman, D.G. (2008). CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet, 371*(9609), 281-283.

Horsman, J., Furlong, W., Feeny, D., & Torrance, G. (2003). The Health Utilities Index (HUI): concepts, measurement properties and applications. *Health and Quality of Life Outcomes, 1*, 54.

Jastreboff, P.J. (1990). Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neurosci Res, 8*(4), 221-254.

Jastreboff, P.J., Gray, W.C., & Gold, S.L. (1996). Neurophysiological approach to tinnitus patients. *American Journal of Otolaryngology, 17*(2), 236-240.

Jastreboff, P.J., & Hazell, J.W. (1993). A neurophysiological approach to tinnitus: clinical implications. *Br J Audiol, 27*(1), 7-17.

Jastreboff, P.J., & Hazell, J.W.P. (2004). *Tinnitus Retraining therapy: Implementing the Neurophysiological Model*. Cambridge: Cambridge University press.

Jastreboff, P.J., & Jastreboff, M.M. (2006). Tinnitus retraining therapy: a different view on tinnitus. *ORL J Otorhinolaryngol Relat Spec, 68*(1), 23-29; discussion 29-30.

Javaheri, S., Cohen, V., Libman, I., & Sandor, V. (2000). Life-threatening tinnitus. *Lancet, 356*(9226), 308.

Johansson, P.A., Farup, P.G., Bracco, A., & Vandvik, P.O. (2010). How does comorbidity affect cost of health care in patients with irritable bowel syndrome? A cohort study in general practice. *BMC Gastroenterology, 10*, 31.

Kahneman, D., Fredrickson, B.L., Schreiber, C.A., & Redelmeier, D.A. (1993). When more pain is preferred to less: Adding a Better End. *Psychological Science, 4*(6), 401-405.

Kahneman, D., Wakker, P., & Sarin, R. (1997). Back to Bentham? Explorations of experienced utility. *Quarterly Journal of Economics, 112*, 375-406.

Kahneman, D. (2000). Experienced Utility and Objective Happiness: A Moment-Based Approach. In D. Kahneman & A. Tversky (Eds.), *Choices, Values and Frames*. New York: Cambridge University Press.

Kahneman, D., Krueger, A.B., Schkade, D.A., Schwarz, N., & Stone, A.A. (2004). A survey method for characterizing daily life experience: the day reconstruction method. *Science, 306*(5702), 1776-1780.

Kahneman. D, & Krueger, A.B. (2006). Developments in the Measurement of Subjective Well-Being. . *Journal of Economic Perspectives, 20*(1), 3-24.

Kaplan, R., & Anderson, J. (1988). The Quality of Well-being scale: rationale for a single quality of life index. In S. Walker, R. Walker & R. Rosser (Eds.), *Quality of life Assessment and Application.* (pp. 51-77). London: MTP Press.

Keeney, R., & Raiffa, H. (1993). *Decisions with multiple objectives: preference and value tradeoffs (2nd edn)*. Cambridge: Cambridge University Press.

Kizilbash, A.H., Vanderploeg, R.D., & Curtiss, G. (2002). The effects of depression and anxiety on memory performance. *Arch Clin Neuropsychol, 17*(1), 57-67.

Knies, S., Ament, A., Evers, S., & Severens, J. (2009). The Transferability of Economic Evaluations: Testing the Model of Welte. *Value in Health, 12*(5), 730-738(739).

Knouse, L.E., Mitchell, J.T., Brown, L.H., Silvia, P.J., Kane, M.J., Myin-Germeys, I. (2008). The expression of adult ADHD symptoms in daily life: an application of experience sampling methodology. *Journal of Attention Disorders 11*(6), 652-663.

Koopmanschap, M.A. (2005). PRODISQ: a modular questionnaire on productivity and disease for economic evaluation studies. *Expert Review of Pharmacoeconomics and Outcomes Research, 5*(1), 23-28.

Kopec, J.A., & Willison, K.D. (2003). A comparative review of four preference-weighted measures of health-related quality of life. *Journal of Clinical Epidemiology, 56*(4), 317-325.

Krog, N.H., Engdahl, B., & Tambs, K. (2010). The association between tinnitus and mental health in a general population sample: results from the HUNT Study. *J Psychosom Res, 69*(3), 289-298.

Kroner-Herwig, B., Frenzel, A., Fritsche, G., Schilkowsky, G., & Esser, G. (2003). The management of chronic tinnitus: comparison of an outpatient cognitive-behavioral group training to minimal-contact interventions. *Journal of Psychosomatic Research, 54*(4), 381-389.

Laird, N.M., & Wang, F. (1990). Estimating rates of change in randomized clinical trials. *Control Clin Trials, 11*(6), 405-419.

Lambeek, L.C., van Tulder, M.W., Swinkels, I.C., Koppes, L.L., Anema, J.R., & van Mechelen, W. (2011). The trend in total cost of back pain in The Netherlands in the period 2002 to 2007. *Spine (Phila Pa 1976), 36*(13), 1050-1058.

Langenbach, M. (2005). Psychological factors in severe disabling tinnitus. *Archives of Otolaryngology - Head & Neck Surgery, 131*(9), 829; author reply 829-830.

Langguth, B. (2012). Tinnitus: the end of therapeutic nihilism. *Lancet, 379*(9830), 1926-1928.

Langguth, B., & Elgoyhen, A.B. (2012). Current pharmacological treatments for tinnitus. *Expert Opin Pharmacother, 13*(17), 2495-2509.

Larson R, Csikszentmihalyi M (1983). The experience sampling method. *New Directions for Methodology of Social and Behavioral Science,15*:41-56.

Leeuw, M., Goossens, M.E., de Vet, H.C., & Vlaeyen, J.W. (2009). The fidelity of treatment delivery can be assessed in treatment outcome studies: a successful illustration from behavioral medicine. *J Clin Epidemiol, 62*(1), 81-90.

Lockwood, A.H., Salvi, R.J., & Burkard, R.F. (2002). Tinnitus. *New England Journal of Medicine, 347*(12), 904-910.

Loewenstein, G.F., & Schkade, D. (1999). Wouldn't it be nice? Predicting future feelings. In D. Kahneman, E. Diener & N. Schwarz (Eds.), *Well-being: Foundations of hedonic psychology* (pp. 85-105). New York: Russell Sage Foundation.

Luo, N., Johnson, J.A., Shaw, J.W., & Coons, S.J. (2009). Relative efficiency of the EQ-5D, HUI2, and HUI3 index scores in measuring health burden of chronic medical conditions in a population health survey in the United States. *Medical Care, 47*(1), 53-60.

Lux-Wellenhof, G., & Hellweg, F.C. (2002, March 2002). *Long-term follow-up study of TRT in Frankfurt.* Paper presented at the Proceedings of the Seventh International Tinnitus Seminar, Perth.

Maes, I.H., Cima, R.F., Vlaeyen, J.W., Anteunis, L.J., & Joore, M.A (2013). Tinnitus: A Cost Study. *Ear & Hearing, 34*(4):508-514.

Maes, I.H., Joore, M.A., Cima, R.F., Vlaeyen, J.W., & Anteunis, L.J. (2011). Assessment of Health State in Patients With Tinnitus: A Comparison of the EQ-5D and HUI Mark III. *Ear & Hearing, 32*(4), 428-435.

Marra, C.A., Esdaile, J.M., Guh, D., Kopec, J.A., Brazier, J.E., Koehler, B.E. (2004). A comparison of four indirect methods of assessing utility values in rheumatoid arthritis. *Medical Care, 42*(11), 1125-1131.

Marra, C.A., Woolcott, J.C., Kopec, J.A., Shojania, K., Offer, R., Brazier, J.E. (2005). A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. *Social Science and Medicine, 60*(7), 1571-1582.

Martinez-Devesa, P., Perera, R., Theodoulou, M., & Waddell, A. (2010). Cognitive behavioural therapy for tinnitus. *Cochrane Database Syst Rev*(9), CD005233.

Martinez Devesa, P., Waddell, A., Perera, R., & Theodoulou, M. (2007). Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews*(1), CD005233.

Maxion-Bergemann, S., Thielecke, F., Abel, F., & Bergemann, R. (2006). Costs of irritable bowel syndrome in the UK and US. *Pharmacoeconomics, 24*(1), 21-37.

McCombe, A., Baguley, D., Coles, R., McKenna, L., McKinney, C., & Windle-Taylor, P. (2001). Guidelines for the grading of tinnitus severity: the results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. *Clinical Otolaryngology and Allied Sciences, 26*(5), 388-393.

McCracken, L.M., Zayfert, C., & Gross, R.T. (1992). The Pain Anxiety Symptoms Scale: development and validation of a scale to measure fear of pain. *Pain, 50*(1), 67-73.

Meeus, O., Blaivie, C., & Van de Heyning, P. (2007). Validation of the Dutch and the French version of the Tinnitus Questionnaire. *B-Ent, 3 Suppl 7*, 11-17.

Meng, Z., Liu, S., Zheng, Y., & Phillips, J.S. (2011). Repetitive transcranial magnetic stimulation for tinnitus. *Cochrane Database Syst Rev*(10), CD007946.

Mesquita, B., Barrett, L.F., & Smith, E.R. (2010). *The mind in context*. New York: Guilford.

Newman, C.W., Jacobson, G.P., & Spitzer, J.B. (1996). Development of the Tinnitus Handicap Inventory. *Archives of Otolaryngology - Head & Neck Surgery, 122*(2), 143-148.

Newman, C.W., Sandridge, S.A., Bea, S.M., Cherian, K., Cherian, N., Kahn, K.M. (2011). Tinnitus: patients do not have to 'just live with it'. *Cleve Clin J Med, 78*(5), 312-319.

Newman, C.W., Sandridge, S.A., & Jacobson, G.P. (1998). Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. *J Am Acad Audiol, 9*(2), 153-160.

Newman, C.W., Wharton, J.A., & Jacobson, G.P. (1997). Self-focused and somatic attention in patients with tinnitus. *J Am Acad Audiol, 8*(3), 143-149.

NICE. (2008). *Guide to the Methods of Technology Appraisals*: London: National Institute for Health and Clinical Excellence.

NIPO. (2002). Tinnitus: Public familiairity and subjective experience. In N. DEPARTMENT OF HEALTH (Ed.). Amsterdam.

Noell, C.A., & Meyerhoff, W.L. (2003). Tinnitus. Diagnosis and treatment of this elusive symptom. *Geriatrics, 58*(2), 28-34.

Nyrop, K.A., Palsson, O.S., Levy, R.L., Korff, M.V., Feld, A.D., Turner, M.J. (2007). Costs of health care for irritable bowel syndrome, chronic constipation, functional diarrhoea and functional abdominal pain. *Alimentary Pharmacology & Therapeutics, 26*(2), 237-248.

Olson, K., O'Brien, M., Rogers, W., & Charness, N. (2011). Diffusion of Technology: Frequency of Use for Younger and Older Adults. *Ageing International 36*(1), 123-145.

Oostenbrink, R., H.A., M., & Essink-Bot, M.L. (2002). The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. *Journal of Clinical Epidemiology, 55*(8), 791-799.

Phillips, J.S., & McFerran, D. (2010). Tinnitus Retraining Therapy (TRT) for tinnitus. *Cochrane Database Syst Rev*(3), CD007330.

Raftery, J. (2001). NICE: faster access to modern treatments? Analysis of guidance on health technologies. *British Medical Journal, 323*(7324), 1300-1303.

Reich, G.D. (2002). The cost of Tinnitus. *Tinnitus Today,* 18-19.

Reis HT (2012). Why researchers should think "real-world": A conceptual rationale. In: Mehl MR, Conner TS (Eds), *Handbook of Research Methods for Studying Daily Life.* New York: The Guilford Press.

Rief, W., Weise, C., Kley, N., & Martin, A. (2005). Psychophysiologic treatment of chronic tinnitus: a randomized clinical trial. *Psychosom Med, 67*(5), 833-838.

Robbins, P., & Aydede, M. (2008). *The Cambridge Handbook of Situated Cognition.* Cambridge: Cambridge University Press

Robinson, M.D., & Clore, G.L. (2002). Belief and feeling: evidence for an accessibility model of emotional self-report. *Psychol Bull, 128*(6), 934-960.

Robinson, R.L., Birnbaum, H.G., Morley, M.A., Sisitsky, T., Greenberg, P.E., & Claxton, A.J. (2003). Economic cost and epidemiological characteristics of patients with fibromyalgia claims. *Journal of Rheumatology, 30*(6), 1318-1325.

Roelofs, J., Peters, M.L., Patijn, J., Schouten, E.G., & Vlaeyen, J.W. (2004). Electronic diary assessment of pain-related fear, attention to pain, and pain intensity in chronic low back pain patients. *Pain, 112*(3), 335-342.

Roelofs, J., Sluiter, J.K., Frings-Dresen, M.H., Goossens, M., Thibault, P., Boersma, K. (2007). Fear of movement and (re)injury in chronic musculoskeletal pain: Evidence for an invariant two-factor model of the Tampa Scale for Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain, 131*(1-2), 181-190.

Rubin, D.B. (1987). *Multiple Imputation for nonresponse in surveys*. New York: John Wiley & Sons.

Rubin, D.C., & Wetzel, A.E. (1996). One Hundred Years of Forgetting: A Quantitative Description of Retention. *Psychological Review, 103*, 734-760.

RVZ. (2006). *Sensible and sustainable care*. Zoetermeer: Council for public health and care

Sackett, D.L., & Torrance, G.W. (1978). The utility of different health states as perceived by the general public. *Journal of Chronical Diseases, 31*(11), 697-704.

Samsa, G., Edelman, D., Rothman, M.L., Williams, G.R., Lipscomb, J., & Matchar, D. (1999). Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics, 15*(2), 141-155.

Schwarz, N. (2011). Why researchers should think "real-time": a cognitive rationale In M. R. Mehl & T. S. Conner (Eds.), *Handbook of research methods for studying daily life* New York: Guilford.

Schwarz, N., Kahneman, D., & Xu, J. (2009). Global and Episodic Reports of Hedonic Experience. In R. Belli, F. Stafford & D. Alwin (Eds.), *Calender and time diary. Methods in Life Course Research* (pp. 157-174). Thousend Oaks: Sage Publications.

Scott, B., & Lindberg, P. (2000). Psychological profile and somatic complaints between help-seeking and non-help-seeking tinnitus subjects. *Psychosomatics, 41*(4), 347-352.

Scott, B., Lindberg, P., Melin, L., & Lyttkens, L. (1990). Predictors of tinnitus discomfort, adaptation and subjective loudness. *British Journal of Audiology, 24*(1), 51-62.

Sculpher, M.J., Claxton, K., Drummond, M., & McCabe, C. (2006). Whither trial-based economic evaluation for health care decision making? *Health Econ, 15*(7), 677-687.

Severens, J.L., Mulder, J., Laheij, R.J., & Verbeek, A.L. (2000). Precision and accuracy in measuring absence from work as a basis for calculating productivity costs in The Netherlands. *Social Science & Medicine, 51*(2), 243-249.

Seydel, C., Haupt, H., Szczepek, A.J., Klapp, B.F., & Mazurek, B. (2010). Long-term improvement in tinnitus after modified tinnitus retraining therapy enhanced by a variety of psychological approaches. *Audiol Neurootol, 15*(2), 69-80.

Snijders, T., & Bosker, R. (1999). *Multilevel analysis: an introduction to basic and advanced multilevel modeling*. London: Sage Publication Ltd.

Spinhoven, P., Ormel, J., Sloekers, P.P., Kempen, G.I., Speckens, A.E., & Van Hemert, A.M. (1997). A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological Medicine, 27*(2), 363-370.

Stiggelbout, A.M., & de Vogel-Voogt, E. (2008). Health state utilities: a framework for studying the gap between the imagined and the real. *Value in Health, 11*(1), 76-87.

Stone AA, Shiffman S (2002). Capturing momentary, self-report data: a proposal for reporting guidelines. *Ann Behav Med. 24*(3):236-43.

Stone, A.A., Schwartz, J.E., Schkade, D., Schwarz, N., Krueger, A., & Kahneman, D. (2006). A population approach to the study of emotion: diurnal rhythms of a working day examined with the Day Reconstruction Method. *Emotion, 6*(1), 139-149.

Stouffer, J. L., & Tyler, R. S. (1990). Characterization of tinnitus by tinnitus patients. *J Speech Hear Disord, 55*(3), 439-453

Sudman, S., Bradburn, N.M., & Schwarz, N. (1996). *Thinking about answers: The application of coginitive processes to survey methodology*. San Francisco: Jossey-Bass.

Tarricone, R. (2006). Cost-of-illness analysis. What room in health economics? *Health Policy, 77*(1), 51-63.

Tay, L., Chan, D., & Diener, E. (in press). The metrics of societal happiness. *Social Indicators Research*.

Terwee, C.B., Dekker, F.W., Wiersinga, W.M., Prummel, M.F., & Bossuyt, P.M. (2003). On assessing responsiveness of health-related quality of life instruments: guidelines for instrument evaluation. *Quality of Life Research, 12*(4), 349-362.

The EuroQol Group. (1990). EuroQol--a new facility for the measurement of health-related quality of life. . *Health Policy, 16*(3), 199-208.

Thewissen, V., Bentall, R.P., Lecomte, T., van Os, J., & Myin-Germeys, I. (2008). Fluctuations in self-esteem and paranoia in the context of daily life. *Journal of Abnormal Psychology, 117*(1), 143-153.

Torrance, G.W., Blaker, D., Detsky, A., Kennedy, W., Schubert, F., Menon, D. (1996). Canadian guidelines for economic evaluation of pharmaceuticals. Canadian Collaborative Workshop for Pharmacoeconomics. *Pharmacoeconomics, 9*(6), 535-559.

Tourangeau, R., Rips, L.J., & Ransinski, K. (2000). *The psychology of survey response*. Cambridge: Cambridge University Press.

Trull TJ, Ebner-Priemer UW (2009). Using experience sampling methods/ecological momentary assessment (ESM/EMA) in clinical assessment and clinical research: introduction to the special section. *Psychol Assess, 21*(4), 457-62.

Ubel, P.A., Loewenstein, G., Hershey, J., Baron, J., Mohr, T., Asch, D.A. (2001). Do nonpatients underestimate the quality of life associated with chronic health conditions because of a focusing illusion? *Medical Decision Making, 21*(3), 190-199.

van Asselt, A.D., Dirksen, C.D., Arntz, A., & Severens, J.L. (2007). The cost of borderline personality disorder: societal cost of illness in BPD-patients. *Eur Psychiatry, 22*(6), 354-361.

Van Breukelen, G.J.P. (2006). ANCOVA versus change from baseline had more power in randomized studies and more bias in nonrandomized studies. *Journal of clinical epidemiology, 59*(9), 920-925.

Van Damme, S., Crombez, G., Bijttebier, P., Goubert, L., & Van Houdenhove, B. (2002). A confirmatory factor analysis of the Pain Catastrophizing Scale: invariant factor structure across clinical and non-clinical populations. *Pain, 96*(3), 319-324.

van den Brink, M., van den Hout, W.B., Stiggelbout, A.M., van de Velde, C.J., & Kievit, J. (2004). Cost measurement in economic evaluations of health care: whom to ask? *Medical Care, 42*(8), 740-746.

Verbeke, G., & Molenberghs, G. (2000). *Linear mixed models for longitudinal data*. New York: Springer.

Vesterager, V. (1997). Tinnitus--investigation and management. *British Medical Journal, 314*(7082), 728-731.

Von Korff, M., & Moore, J.C. (2001). Stepped care for back pain: activating approaches for primary care. *Ann Intern Med, 134*(9 Pt 2), 911-917.

Von Neumann, J., & Morgenstern, O. (1944). *Theory of games and economic behaviour*. Princeton: Princeton University Press.

Walen, H.R., Cronan, P.A., & Bigatti, S.M. (2001). Factors associated with healthcare costs in women with fibromyalgia. *American Journal Managed Care, 7 Spec No*, SP39-47.

Weinstein, N.D. (1992). Community noise problems: Evidence against adaptation. *Journal of Environmental Psychology, 2*(2), 87-97.

White, M.P., & Dolan, P. (2009). Accounting for the richness of our daily activities. *Psychological Science, 20*(8), 1000-1008.

Wolfe, F., Anderson, J., Harkness, D., Bennett, R.M., Caro, X.J., Goldenberg, D.L. (1997). A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis & Rheumatism, 40*(9), 1560-1570.

Wolfs, C.A., Dirksen, C.D., Kessels, A., Severens, J.L., & Verhey, F.R. (2009). Economic evaluation of an integrated diagnostic approach for psychogeriatric patients: results of a randomized controlled trial. *Arch Gen Psychiatry, 66*(3), 313-323.

World Health Organization. (1946). CONSTITUTION of the World Health Organization. *Public Health Rep, 61*, 1268-1279.

Zachriat, C., & Kroner-Herwig, B. (2004). Treating chronic tinnitus: comparison of cognitive-behavioural and habituation-based treatments. *Cognitive Behaviour Therapy 33*(4), 187-198.

Zautra, A. J., Johnson, L. M., & Davis, M. C. (2005). Positive affect as a source of resilience for women in chronic pain. *J Consult Clin Psychol, 73*(2), 212-220.

Zenner, H. P., & Zalaman, I. M. (2004). Cognitive tinnitus sensitization: behavioral and neurophysiological aspects of tinnitus centralization. *Acta Otolaryngology, 124*(4), 436-439

Zirke, N., Seydel, C., Szczepek, A.J., Olze, H., Haupt, H., & Mazurek, B. (2013). Psychological comorbidity in patients with chronic tinnitus: analysis and comparison with chronic pain, asthma or atopic dermatitis patients. *Qual Life Res, 22*(2), 263-272.

Zoger, S., Svedlund, J., & Holgers, K.M. (2006). Relationship between tinnitus severity and psychiatric disorders. *Psychosomatics, 47*(4), 282-288.

SAMENVATTING

Het algemene doel van dit proefschrift was om de invloed van tinnitus op gezondheid gerelateerde kwaliteit van leven en kosten te evalueren. Ook werd de effectiviteit van een gespecialiseerde trapsgewijze cognitieve gedragstherapie (CGT) behandeling vergeleken met de gebruikelijke zorg. Hoofdstuk 1 t/m 4 zijn gebaseerd op data van een gerandomiseerd gecontroleerde trial (RCT). Hoofdstuk 5 en 6 zijn gebaseerd op een studie waarin de Experience Sampling Method (ESM) is gebruikt om (aspecten van) gezondheid gerelateerde kwaliteit van leven in het dagelijkse leven te meten.

In hoofdstuk 1 werden utiliteitsscores gemeten in een populatie patiënten met tinnitus met twee utiliteitsinstrumenten: de EuroQol 5D (EQ-5D) en de Health Utilities Index Mark III. Deze instrumenten verschillen in de conceptualisatie en operationalisering van gezondheid en de waarderingsmethode waarop de utiliteitscores worden gebaseerd. Overeenstemming, constructvaliditeit en responsiviteit van beide meetinstrumenten werden onderzocht om te bepalen welk instrument de voorkeur heeft bij tinnitus patiënten. Corresponderende dimensies van beide maten lieten hoge correlaties zien, maar bij de EQ-5D werd veel vaker een plafondeffect gevonden. De HUI Mark III utiliteitsscores waren lager dan de EQ-5D utiliteitsscores en de overeenstemming was matig tot slecht. Zowel de EQ-5D als de HUI Mark III vertoonden tekenen van constructvaliditeit en beide maten lieten een statistisch significante verandering in de gemiddelde utiliteitsscores van verbeterde patiënten zien na drie maanden behandeling. De HUI Mark III is het meest sensitief voor verandering in patiënten met tinnitus. Er werd geconcludeerd dat ondanks aanzienlijke overlap tussen beide instrumenten, de HUI Mark III het beste utiliteitsinstrument is voor patiënten met tinnitus.
In hoofdstuk 2 werd de maatschappelijke ‘cost-of-illness’ (COI) van tinnitus in Nederland bepaald. De berekeningen werden ‘bottom-up’ uitgevoerd waarbij de consumptie van gezondheidszorg en gegevens over kosten werden gemeten met behulp van een kostenvragenlijst onder patiënten in een steekproef en vervolgens geëxtrapoleerd naar de gehele Nederlandse bevolking. Daarnaast werd de impact van demografische en ziekte kenmerken op de gezondheidszorgkosten en de maatschappelijke kosten onderzocht. De gemiddelde maatschappelijke ‘cost of illness’ was €6.7 miljard, of €5,315 per patiënt per jaar. Sensitiviteitsanalyses lieten zien dat verschillen in prevalentie van tinnitus vooral de maatschappelijke kosten beïnvloedde. De gezondheidszorgkosten varieerden van €1.0 miljard tot 2.9 miljard, terwijl de maatschappelijke kosten varieerden van €3.3 miljard tot €10.0 miljard. Gerapporteerde ernst van de tinnitus was de belangrijkste positieve voorspeller van gezondheidszorgkosten en maatschappelijke kosten. Andere significante voorspellers waren duur van klachten, depressieve scores en leeftijd (alleen voor maatschappelijke kosten). Er werd geconcludeerd dat de economische last van tinnitus substantieel is.
In hoofdstuk 3 werd de effectiviteit van een nieuw gespecialiseerd stapsgewijs multidisciplinair protocol (SC) vergeleken met de gebruikelijke zorg voor tinnitus (UC). De eerste stap van de SC bestond uit audiologische diagnostiek en revalidatie, begeleiding gebaseerd op Tinnitus Retraining Therapy, psycho-educatie en psychologische analyse en advies. De tweede stap van de SC bestond uit begeleiding, psycho-educatie, toegepaste relaxatie, CGT, elementen van acceptance and commitment therapy en mindfullness. De eerste stap van de UC bestond vooral uit audiologische diagnostiek en revalidatie zoals het voorschrijven van hoortoestellen en tinnitusmaskeerders. De tweede stap van de UC bestond indien noodzakelijk uit een of meerdere consulten bij een maatschappelijk werker met een maximum van tien sessies van 60 minuten. Een RCT werd uitgevoerd met 492 volwassen tinnitus patiënten waarvan er 247 werden toegewezen aan de UC en 245 aan de SC. Alle patiënten werden gestratificeerd op ernst van de tinnitus en gehoorverlies. De primaire uitkomsten waren gezondheid gerelateerde kwaliteit van leven (HUI Mark III), tinnitus ernst (TQ), en beperking door de tinnitus (THI). Secundaire uitkomstmaten waren negatief affect

(HADS), catastrofale misinterpretatie (TCS) en angst voor tinnitus (FTQ). Metingen vonden plaats voor behandeling en 3, 8 en 12 maanden na randomisatie. Multilevel regressie technieken werden gebruikt om de data te analyseren. De analyse toonde aan dat de SC meer effectief was dan de UC met betrekking tot het verbeteren van kwaliteit van leven, het verminderen van tinnitus ernst en ervaren beperkingen door de tinnitus. Bovendien liet de SC betere resultaten zien dan de UC met betrekking tot verbeteringen in algemene negatieve emotionele toestand, niveau van tinnitus gerelateerd catastrofaal denken, en tinnitus gerelateerde angst.

Hoofdstuk 4 bepaalde de kosteneffectiviteit van de SC vergeleken met de UC vanuit een maatschappelijk perspectief naast de bovengenoemde RCT. De berekening van de maatschappelijke kosten was gebaseerd op metingen uit een kostenvragenlijst en Nederlandse standaard prijzen of andere bronnen als deze niet aanwezig waren. De voor kwaliteit van leven gecorrigeerde levensjaren (QALYs) werden gebaseerd op metingen met de HUI Mark III. Totale gemiddelde gebootstrapte kosten ware €5,636 in de UC en €5,921 in de SC. Kosten geassocieerd met de tinnituszorg in het audiologische centrum waren behoorlijk hoger in de SC. Dit werd deels gecompenseerd door lagere kosten in de SC voor andere tinnitus gerelateerde gezondheidszorgkosten. Productiviteitskosten waren hoger in de SC. De resultaten toonden dat SC de maatschappij €19,688 kost per gewonnen QALY. De waarschijnlijkheid dat de SC kosteneffectief is vanuit een maatschappelijk perspectief, is 58% als de maatschappij bereidheid zou zijn om €35,000 voor een QALY te bepalen. De NICE richtlijn stelt dat de vergoeding van een interventie die minder kost dan £30,000 (ongeveer €45,000) over het algemeen nooit wordt betwist. De Nederlandse raad voor volksgezondheid en zorg (RVZ) heeft de drempel vastgesteld op €80,000 voor ziekten met een hoge last. Gebaseerd op deze gegevens werd SC gezien als meer kosteneffectief dan UC. Echter, de onzekerheid rond de incrementele kosten en effecten was aanzienlijk.

Hoofdstuk 5 exploreerde de mogelijke waarde van het verkrijgen van een momentane, in plaats van een retrospectieve beschrijving en waardering van de eigen gezondheid gerelateerd kwaliteit van leven (HRQOL) van een persoon. De studiepopulatie bestond uit 139 deelnemers. Om een verscheidenheid aan ervaren gezondheidstoestanden te waarborgen werden deelnemers gerekruteerd uit drie verschillende patiënten populaties (lichamelijke klachten met een bekende oorzaak, lichamelijke klachten zonder bekende oorzaak en psychologische klachten) en een steekproef van het algemene publiek. Momentane HRQOL, positief affect (PA, negatief affect (NA) en fysieke symptomen (PS) werden onderzocht met de Experience Sampling Method (ESM). De ESM bestond uit een zogenaamde beep vragenlijst die 10 keer per dag at random werd afgenomen. Bivariate correlaties en multilevel analyses werden gebruikt om de relatie tussen momentane HRQOL en momentane PA, NA en PS te onderzoeken. Met betrekking tot de uitvoerbaarheid, was de algemene primaire participatie laag maar er waren geen uitvallers en het aantal afgeronde vragenlijsten was vergelijkbaar met dat van andere studies. De analyses lieten zien dat PA, NA en PS, momentane HRQOL voorspellen. Ook werd er gevonden dat deze relaties sterker zijn bij patiënten met psychologische klachten (PA, NA en PS) en tinnitus (PA en PS), dan bij patiënten met lichamelijke klachten en personen van de algemene populatie. Multiple regressie analyses lieten zien dat bij het toevoegen van interactietermen aan het model, geen enkele momentane gevoelens en symptomen significante voorspellers waren van de EQ VAS. Dit steunt eerdere bevindingen dat een globale rapportage van gezondheid in het verleden meer aansluit bij ‘beliefs’ (semantisch geheugen) dan op specifieke gevoelens en symptomen. We concludeerden dat het gebruik van de ESM om momentane ervaring van gezondheid in verschillende populaties uitvoerbaar is. De resultaten lieten zien dat binnen personen de waardering van globale gezondheid HRQOL en specifieke symptomen variabel zijn van

moment tot moment. Ook verschilt de relatie tussen specifieke momentane gevoelens en symptomen en de momentane waardering van HRQOL per populatie.
In hoofdstuk 6 was het doel om patiënten met tinnitus te vergelijken met een steekproef van het algemene publiek met betrekking tot emoties, activiteiten en sociale interacties in het dagelijkse leven zoals die gemeten werden met de ESM. Hoewel er enige kennis is over deze relaties vanuit eerder onderzoek, hebben deze studies allemaal gebruik gemaakt van retrospectieve vragenlijsten over gebeurtenissen uit het verleden wat kan leiden tot verschillende soorten onzuiverheden in de metingen. Binnen de patiënten met tinnitus werd gekeken naar de associatie tussen van tinnitus ernst en het niveau van PA, NA, PS, activiteiten en sociale interactie in het dagelijkse leven. Veertig patiënten met tinnitus en een steekproef van veertig personen van het algemene publiek werden geïncludeerd in deze studie. Multilevel analyses bevestigden een significant verschil tussen de steekproeven met betrekking tot PA, NA en PS, maar niet met betrekking tot activiteiten en sociale interacties. Als tinnitus werd ervaren als meer ernstig, was er een gelijktijdig verhoging in pijn en vermoeidheid. Daarnaast ging meer ernstige tinnitus gepaard met meer negatieve en minder positieve stemming. De time-lagged analyses lieten zien dat pijn een positieve associatie heeft met tinnitus op een moment, maar een negatieve associatie met tinnitus op het volgende moment. Dit betekent dat het effect van pijn op tinnitus vermindert over de tijd. Dit kan wijzen op gewenning aan pijn. Verder was er een omgekeerd tijdelijk effect van tinnitus intensiteit op navolgende pijn en positief affect. Dit betekent dat het negatieve effect van tinnitus op pijn en positief affect afneemt over de tijd wat wijst op gewenning aan de tinnitus.
Er kan worden geconcludeerd dat tinnitus een belangrijke impact heeft op emoties en symptomen in het dagelijkse leven.

DANKWOORD

Eindelijk is het klaar: mijn boekje is af! Nu is de tijd aangebroken om te reflecteren op een fantastische tijd waarin ik veel heb geleerd en vele bijzondere mensen heb mogen ontmoeten. Dit boekje was niet tot stand gekomen zonder een aantal van hen.

Allereerst dank aan alle patiënten die hebben meegedaan aan dit onderzoek en vaak vele vragenlijsten hebben ingevuld. Daarnaast dank aan alle medewerkers van Adelante, PsyQ en het azM die betrokken zijn geweest bij de inclusie van al deze patiënten.

Ten eerste wil ik graag mijn promotieteam bedanken, te weten mijn copromotoren Manuela Joore en Lucien Anteunis en mijn promotoren Madelon Peters en Bernd Kremer. Manuela, zonder jou was dit proefschrift er niet geweest. Jouw kennis en ideeën over de gezondheidszorg, en in het bijzonder HTA, is volgens mij door niemand te evenaren. Je hebt daarbij ook nog de gave om de meest ingewikkelde zaken op een begrijpelijke manier uit te leggen. Ik ben dankbaar voor alles wat ik van je heb mogen leren, zowel op professioneel als op persoonlijk vlak. Ik hoop dat er een vervolg komt voor ons kwaliteit van leven project zodat we nog heel lang kunnen samenwerken. Lucien, het is een feestje om met je samen te werken. Bij alle problemen die tijdens het tinnitus project op ons pad zijn gekomen was jij degene die rust en perspectief bracht in het geheel. Daarnaast wacht er, mede dankzij jou, na mijn opleiding, een nieuwe uitdaging op mij bij het audiologisch centrum. Bedankt voor alles! Madelon, je kwam later bij het team als promotor en daar ben ik nog steeds heel blij mee. Door jouw bemoeienis heeft de ESM studie voor mij meer diepgang gekregen. Ik wil je bedanken voor de prettige samenwerking en je altijd kritische en zeer waardevolle advies. Bernd, bedankt voor je bijdrage aan dit proefschrift.

De leden van de beoordelingscommissie, voorzitter Prof. dr. Carmen Dirksen, prof. dr. Silvia Evers, prof. dr. Inez Myin-Germeys, dr. Carsten Leue en prof. dr. Robert Stokroos, wil ik bedanken dat ze bereid zijn om zitting te nemen in de commissie en het concept proefschrift van commentaar te voorzien.

Rilana, aan jouw enthousiasme en overtuiging kunnen veel mensen een voorbeeld nemen. Bedankt dat ik aan je zijde heb mogen staan bij dit project; ik denk dat we trots kunnen zijn op het resultaat!

Marianne Nelis, jij was degene die het ESM project draaiende hield toen ik dat door persoonlijke omstandigheden niet kon. Door jou kon ik er blind op vertrouwen dat de dataverzameling precies zo zou verlopen als ik wilde en misschien nog wel beter: bedankt daarvoor!

De overige coauteurs wil ik ook bedanken voor hun waardevolle bijdragen aan de verschillende publicaties. In het bijzonder dank aan Johan Vlaeyen, Philippe Delespaul en Koen Schruers. Johan, bedankt voor je betrokkenheid bij het tinnitus project en je altijd bemoedigende woorden. Philippe, jij verdient een hele dikke dankjewel. Ondanks jouw drukke agenda heb je vaak op korte termijn tijd voor me vrij gemaakt om de meest triviale vragen over multilevel analyses en andere ESM-zaken te beantwoorden. Mede dankzij jou zijn de uiteindelijke ESM-papers naar een hoger plan getild! Koen, jij maakte het niet alleen mogelijk om bij PsyQ patiënten te werven, maar je gaf mij ook het vertrouwen om daar als psycholoog aan de slag te gaan. Hoewel dit van korte duur was, heb ik er veel van geleerd. Bedankt!

Aan alle collega's van KEMTA. Ten eerste mijn kamergenootje Mirjam, ik ben dankbaar dat jij er was om mee te 'zeuren', mee te lachen en zelfs om mee te huilen. Dankzij jou ging ik aan het einde van de dag meestal met een glimlach naar huis. Bedankt daarvoor. En dan mijn kamergenootjes Denise en Annemieke. Ook dankzij jullie kan ik terug kijken op een geweldige promotietijd. Wat hebben we veel lol gehad: met elkaar en om elkaar. Sanne, een kamergenoot voor korte tijd, maar een vriendin voor het leven; bedankt voor je steun. Cecile, bedankt voor de gezellige tijd op die enorm saaie luchthaven in Berlijn en voor je hulp bij de laatste en zwaarste loodjes! Maar ook Irene, Brigitte, Thea, Fons, Carmen en alle andere collega's van KEMTA: bedankt voor een onvergetelijke tijd!

En dan aan alle collega's van het AC (Adelante). Op verschillende manieren zijn jullie betrokken geweest bij het tinnitus project. Bianca, Karin, Paulien en Marieke, bedankt voor de praktische ondersteuning bij het tinnitus project. Dyon, Ingrid, Nele, Math en Lobke, ook jullie verdienen om verschillende redenen een dankjewel!

En dan wil ik nog graag de mensen bedanken die niet inhoudelijk betrokken waren maar die mij wel enorm hebben gesteund de afgelopen jaren. Mijn lieve vrienden, buren en (schoon)-familie waar ik vele leuke momenten mee heb mogen beleven. Ik prijs me gelukkig met zoveel lieve mensen om me heen.

Mijn collega's bij de medische psychologie en opleidingsgenootjes van de GZ-opleiding, in het bijzonder Nancy, Suzanne, Annette & Sabrine. Jullie betrokkenheid, vrolijkheid en enthousiasme hebben ervoor gezorgd dat het afgelopen jaar niet alleen druk was maar ook ontzettend leuk en leerzaam.

Lydia & Roy, we leerden elkaar kennen op de NICU, nu alweer bijna 3 jaar geleden. Ik ben erg dankbaar dat uit deze moeilijke periode, zo'n fijne vriendschap is ontstaan en ik ben er dan ook trots op dat jij, Lydia, de omslag van mijn proefschrift hebt ontworpen. Bedankt!

Sandy, vriendinnetje van het eerste uur. Jouw vrolijke en positieve kijk op de wereld zijn een voorbeeld voor mij. Je bent op verschillende momenten een grote steun voor mij geweest. Ik hoop dat onze vriendschap voor altijd mag blijven duren en dat jouw droom heel snel werkelijkheid mag worden.

Cindy en Aimée, bedankt dat jullie vandaag aan mijn zijde staan. Mede dankzij jullie ben ik zelf niet verworden tot patiënt. Cindy, we hebben er samen al een half leven op zitten. Van rebelleren in groep 5 tot het eindexamen van Stella Maris. Van vele stapavonden in 'De Smid' in Reijmerstock tot het uitwisselen van ervaringen als moeder; ik kan me gewoon niet voorstellen hoe mijn leven er had uit gezien zonder jou. Aimée, soms botsen onze karakters, maar altijd vinden we onze weg terug naar elkaar. Omdat ik peettante mocht worden van je prachtige dochter Misja, en omdat je gewoon een fantastisch mens bent.

Andy, grote broer, ik bewonder jou om je eeuwige doorzettingsvermogen en ik ben trots op wat je hebt bereikt. Bedankt dat je ondanks je drukke schema altijd tijd voor me hebt vrij gemaakt om mij te helpen bij het oplossen van allerlei digitale problemen.

Lieve oma Käthe, onzichtbaar aan mijn zijde. Ondanks dat je al lang niet meer in ons midden bent hoor jij in dit dankwoord. Jij legde samen met pap en mam de basis. Ik hoop dat je trots op me bent!

Lieve pap & mam, dit boekje is opgedragen aan jullie. Omdat ik altijd onvoorwaardelijk op jullie kan terugvallen, omdat jullie me vrij hebben gelaten om mijn eigen keuzes en fouten te maken, omdat jullie fantastische grootouders zijn voor Mila en Elin… en zo kan ik nog oneindig veel redenen noemen waar ik jullie nooit genoeg voor kan bedanken. Ik hou van jullie!

Elin en Mila, mijn prachtige, lieve meisjes. Jullie maken het leven zoveel leuker! Dit boekje is ook opgedragen aan jullie, omdat er zoveel meer is in het leven dan promoveren en carrière maken. Ik geniet van alles wat jullie doen, en kijk elke dag met verwondering naar de manier waarop jullie, ieder op je eigen manier, de wereld ontdekken. Ik ben dankbaar dat ik jullie mama mag zijn.

Lieve Radek, het laatste woord richt ik aan jou. Hoge pieken en diepe dalen hebben we de afgelopen jaren samen overleefd, met als absoluut hoogtepunt de dag dat onze meiden thuis kwamen uit het ziekenhuis. Zonder jou had ik na deze periode niet de kracht gevonden om dit boekje af te schrijven. Altijd heb je mij gesteund en gestimuleerd en nooit heb je geklaagd als ik weer eens achter de computer moest of als het me even teveel werd. Lieve schat, bedankt voor alles!

CURRICULUM VITAE

Iris Maes was born on June 5th 1982 in Sittard (The Netherlands). She graduated in 2000 from Stella Maris College in Meerssen. In September 2001 she started studying Psychology at Tilburg University and she received her master's degree in May 2006. After a few months she started working as a psychologist at Prins Claus Centrum in Sittard. At the end of 2007 she started as a clinical psychologist at Adelante, audiology and communication, combined with a part-time PhD trajectory at the department of Clinical Epidemiology and Medical Technology Assessment of the Maastricht University Medical Centre and the department of Clinical Psychological Science of Maastricht University. In 2010 she started working as a psychologist at the Academic Anxiety Centre of Mondriaan (PsyQ). In 2013 she started with a two-year post-graduate training at the department Medical Psychology of the Maastricht University Medical Centre to become a registered GZ-psychologist.

Iris is married to Radek Nowak. They have two children: Elin (2010) and Mila (2010)

Publications

Cima R.F., Joore M.A., Maes I.H., Anteunis L.J., Vlaeyen J.W. (2009). Cost-effectiveness of multidisciplinary management of Tinnitus at a specialized Tinnitus centre. *BMC Health Services Research*; 9: 29.

Maes I.H., Joore M.A., Cima R.F., Vlaeyen J.W., Anteunis L.J. (2011). Comparison of EQ-5D and HUI3 in patients with tinnitus. *Ear & Hearing*; 32 (4): 428-35.

Cima R.F., Vlaeyen J.W., Maes I.H., Joore M.A., Anteunis L.J. (2011). Tinnitus interferes with daily life activities: a psychometric examination of the tinnitus disability index. *Ear and Hearing*, 32(5), 428-35.

Cima, R.F., Maes I.H., Joore, M.A., Scheyen D.J.W.M., Elf Refaie A., Baguley D.M., Anteunis L.J.C., van Breukelen, G.J.P., Vlaeyen J.W.S. (2012). Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. The Lancet; 379: 1951-59.

Maes I.H., Cima R.F., Vlaeyen J.W., Anteunis L.J., Joore M.A. (2013). Tinnitus: a cost study. Ear & Hearing; 34 (4): 508-14.

Maes I.H.L., Cima R.F.F., Anteunis L.J.C, Scheijen D.J.W.M., Baguley D.M., El Refaie A., Vlaeyen J.W., Joore M.A (2013). Cost-effectiveness of specialized treatment based on cognitive behavioural therapy versus usual care for tinnitus. Accepted for publication in Otoloy and Neurotology.

Maes I.H., Peters M.L., Delespaul Ph.A.E.G., Anteunis L.J.C., Joore M.A. (2013). The effects of tinnitus on daily life: an experience sampling study. Submitted for publication.

Maes I.H., Delespaul Ph.A.E.G, Peters M.L., White M.P., Horn Y. van, Schruers K, Anteunis L.J.C., Joore M.A (2013). Measuring Health Related Quality of Life by Experiences: the Experience Sampling Method. Submitted for publication.

Cima, R.F., van Breukelen, G.J.P., Maes I.H., Joore, M.A., Anteunis L.J.C., Vlaeyen J.W.S. (2013). Tinnitus-related fear mediates the effects of a CBT-based specialized tinnitus treatment. Submitted for publication.

Presentations

Maes I.H.L, Delespaul Ph.A.E.G., White M., Anteunis L.J.C., Joore M.A. (2012). Experience sampling to obtain health state valuations. Accepted as poster presentation at ISPOR European Congres, Berlin, Germany.

Maes I.H.L., Cima R.F.F., Anteunis L.J.C, Scheijen D.J.W.M., Baguley D.M., El Refaie A., Vlaeyen J.W., Joore M.A (2012)**.** Cost-effectiveness of specialized treatment based on cognitive behavioural therapy versus usual care for tinnitus. Accepted as poster presentation at ISPOR European Congres, Berlin, Germany.

Maes I.H., Joore M.A., Cima R.F., Vlaeyen J.W., Anteunis L.J. (2009). Response shift in patients with tinnitus. Oral presentation at 7th world congress of the international Health Economics Association (iHEA), Beijing, China.

Maes I.H., Joore M.A., Cima R.F., Vlaeyen J.W., Anteunis L.J. (2008). Comparison of EQ-5D and HUI3 in patients with tinnitus. ISPOR European Congress, Athens, Greece. Value in Health; 11 (6): A347.